

**Neuropsychological assessment of executive functions in  
substance dependence populations: A systematic review**

by

JACQUES JANSEN VAN VUUREN

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## **ABSTRACT**

The role of executive functioning in substance dependence and addiction has received increased attention in recent years; however, the findings of empirical studies are at times contradictory and difficult to compare at face value. To address the current state of fragmentation and to delineate the current body of knowledge a systematic review of existing studies was conducted. The synthesis of the findings from these studies confirmed that lower neuropsychological performance scores of executive functioning are observed in substance dependent populations. Furthermore, the synthesis of the components of these studies provided a comprehensive overview and revealed a number of critical gaps in the current body of knowledge. The gaps include limitations concerning specific demographics of the samples studied (under-representation of females, adolescents, the elderly, individuals with limited education, and individuals from Africa, Oceania, Asia, Latin America and the Caribbean), as well as the scarce number of studies investigating specific substances; insufficient longitudinal studies; and the fragmentation of executive functioning as a theoretical construct.

### **KEY TERMS:**

Neuropsychological Assessment; Executive Functions; Substance Dependence; Addiction; Systematic Review; Cognition; Attention; Working Memory; Decision Making; Wisconsin Card Sorting Test; Stroop; Trail Making Test

## DECLARATION

Name: Jacques Jansen van Vuuren

Student number: 43876226

Degree: Master of Arts in Psychology

Exact wording of the title of the dissertation as appearing on the electronic copy submitted for examination:

### **NEUROPSYCHOLOGICAL ASSESSMENT OF EXECUTIVE FUNCTIONS IN SUBSTANCE DEPENDENCE POPULATIONS: A SYSTEMATIC REVIEW**

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I further declare that I submitted the dissertation to originality checking software and that it falls within the accepted requirements for originality.

I further declare that I have not previously submitted this work, or part of it, for examination at Unisa for another qualification or at any other higher education institution.

  
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# **Chapter 1: Introduction**

## **1.1 Introduction**

In this chapter, I provide an overview of the main themes that are investigated in this dissertation and place them within a broader contextual background. The problem statement is presented, together with the research questions and objectives. An overview of the methodology used in the study is provided, the significance of the study is discussed, and the structure of the systematic review is outlined.

## **1.2 Background**

This research study is a systematic review of existing empirical studies that report on performance measures of executive functioning, by means of neuropsychological assessment techniques, in substance dependence populations. The predefined protocol for the systematic review is available in Appendix A.

Substance dependence remains a global problem and continuous efforts are underway by leading world organisations to reduce the detrimental effects of this phenomenon (United Nations Office on Drugs and Crime, 2019). Substance dependence is harmful to both the affected individual and society at large. For the individual, this harm manifests in various ways, including physiological damage, psychological distress, social and occupational dysfunction and overall impairment in quality of life (American Psychiatric Association, 2013; World Health Organization, 2019). The reported prevalence of other psychiatric comorbidities is also very high (Abou-Saleh & Janca, 2004; DeVito et al., 2016; Kingston et al., 2017). Substance dependence is also strongly related to harmful socioeconomic issues such as violence, crime, road accidents, lost work productivity and health care costs (Gowing et al., 2015; Johnson & Belfer, 1995; United Nations Office on Drugs and Crime, 2019; World Health Organization, 2016). The global prevalence of substance dependence, as reported by the United Nations Office on Drugs and Crime (2019) is alarming: approximately 5.5 per cent of the global population, or one in every 18 people, have used drugs in the previous year and an estimated 35 million people suffer from substance dependence and require treatment (United Nations Office on Drugs and Crime, 2019).

Individuals with substance dependence are regarded as suffering from a disease known as addiction. This disease is chronic and characterised by neurofunctional impairment (American Society of Addiction Medicine, 2018; World Health Organization, 2019). Although the main emphasis in research has been on the impairment of the reward-circuitry, other domains, such as executive functioning, have received increasing attention in recent years (Verdejo-García, 2017). This is because the importance of the relationship between executive functioning, addiction and substance dependence has been demonstrated and theoretical models have been developed that describe this relationship (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Goldstein & Volkow, 2011; Koob & Volkow, 2016; Lewis, 2018).

Executive functioning is a theoretical construct, with a history in the fields of psychology and neuroscience (Goldstein, et al., 2014). This multifaceted mental faculty is made up of various mental sub-domains and serves as a functional system that allows the individual to continually and efficiently adapt to the environment by means of future-oriented, goal-directed behaviours (Jurado & Rosselli, 2007; Lezak et al., 2012). Some of the sub-domains of executive functioning include decision making, working memory and attention (Fuster, 2017). However, depending on the level of analysis, executive functioning can be comprised of a multitude of sub-domains. To understand these constructs and their role in both health and disease, neuropsychological assessment instruments have been developed. These standardised instruments measure observable behaviour to make inferences about mental faculties that cannot be observed directly (Lezak et al., 2012). These measurement techniques continuously improve and new tools are developed with advances in science and technology.

### **1.3 Problem Statement**

The findings of existing empirical studies related to executive functioning and substance dependence are at times contradictory and difficult to compare at face value. More specifically, the status of the existing body of knowledge is unclear in terms of potential gaps and exhaustive evidence. In addition, related research, in the form of existing systematic reviews, indicates that the heterogeneity of empirical studies is very high. Some of the main reasons include the assessment of diverse population samples, different substance use behaviours, the use of different assessment measures, the measurement of different constructs or different theoretical levels of analysis (Cohen &

Weinstein, 2018; Crean et al., 2011; Potvin et al., 2018; Stevens et al., 2014). The same lack of clarity is evident in the field of executive functioning. Research of executive functioning has rapidly grown into a vast area of neuroscience with high fragmentation into separate niches and sub-niches, often with little interaction (Goldberg, 2017). Also, the numerous conceptual models or frameworks (Chan et al., 2008; Jurado & Rosselli, 2007) with disagreement in constructs, scope and level of analysis (Goldberg, 2017; Goldstein et al., 2014; Miyake & Friedman, 2012) contribute to the heterogeneity in existing reviews. This makes evidence synthesis difficult and at times impossible. These ambiguities and contradictions in the literature need to be explored and delineated.

## **1.4 Study Aims and Objectives**

The main objectives of the systematic review are to identify the available empirical studies related to substance dependence and the neuropsychological assessment of executive functions and, by the use of appropriate methods, to analyse and synthesise the evidence in order to delineate the current body of knowledge and address the current state of fragmentation. This is accomplished by answering the following predefined review questions:

- Which substance dependent populations have been assessed using neuropsychological measures for executive functioning?
- Which assessments and batteries were used to measure executive functioning?
- What comparators were used in the respective studies?
- What are the findings of the neuropsychological assessment measures?
- In what settings were assessments conducted?
- Which study designs were used?
- What is the risk of bias within the respective studies?
- What are the key consensus or near-consensus findings regarding the relationship between executive functions and substance dependence?
- Are there any marked differences or inconsistencies between studies?
- What are the strengths and limitations of the study designs that were used?
- Are there any controversial issues?
- Is exhaustive evidence provided or are there gaps and a need for further research?

## **1.5 Significance of the Study**

The systematic review methodology is considered the gold standard way to synthesise studies informing the same research problem or questions. Currently, no systematic review exists with the scope of the current study. In terms of the problems identified, this study aims to contribute by investigating the manner and extent to which impairment in executive functioning plays a role as a risk factor in substance dependence and addiction. Additionally, the study aims to identify contradictions in research studies and possible reasons for these, including theoretical fragmentation, methodological aspects and heterogenic factors. The results from this review may contribute to our understanding of substance dependence, neuropsychological assessment and executive functioning and the impairment of executive functioning as a risk factor in addiction. The possible gaps and exhaustive evidence revealed by a systematic review of the available literature may also guide future research.

## **1.6 Overview of the Methodology**

A systematic review involves synthesising large bodies of previously conducted (and usually published) research and as such is typically grounded in an empirical research paradigm in that data is gathered and analysed in an objective manner. However, the types of previous research that is synthesised does not have to be limited to empirical work, but could, for example, include qualitative case studies, grounded theory research, and the like. For the current review only studies conducted within a broadly empirical frame are included.

In terms of methods, a systematic review follows stages that are well-defined and transparent. This ensures the legitimacy of the identification of available data. It also ensures the accurate synthesis of the findings to provide relevant conclusions. The key elements of the systematic review methodology are: (1) a pre-defined protocol, (2) an exhaustive literature search, (3) the screening and selection of studies using specified inclusion and exclusion criteria, (4) data extraction of the included studies, (5) quality assessment, and (6) the analysis and synthesis of the extracted data (Boland et al., 2017; Gough et al, 2012).

Regarding ethical considerations, these may arise where the review is, for example, based on confidential or embargoed previous work, but the current review is limited to

work that had previously been published in the academic literature, and where further review and scrutiny by peers are therefore implicitly invited.

## **1.7 Chapter Overview**

In **Chapter 2**, a theoretical review is presented to provide a context for the systematic review. This serves as both a conceptual framework for the research study and a primer for the reader. The main themes that are discussed include substance dependence, neuropsychological assessment and executive functioning.

**Chapter 3** presents the general research approach adopted, as well as the specifics of how it was applied to the current study. Systematic reviews are still relatively uncommon in psychology and, therefore, I present the conceptual basics of systematic review methodology in some detail, together with a description of the techniques of applying it in practice. In the second part of the chapter, I describe the procedures followed in the systematic review with detailed explanations of each step in the process.

The results are reported in **Chapter 4** by describing how the extracted data from the 390 studies was synthesised and presenting the subsequent findings. These findings include the demographics and other characteristics of the population samples; the methods for diagnostic and neuropsychological assessment; the general study characteristics such as study designs, settings and countries; and finally, the results pertaining to executive functioning and substance dependence.

**Chapter 5** presents a discussion of the results and of the conclusions that can be drawn from them. Key findings are highlighted and the strengths and limitations of the review are outlined. Lastly, the identified gaps in and implications of these findings are outlined.

## **Chapter 2: Literature Review**

### **2.1 Introduction**

In this chapter, I present a theoretical review to provide a context for the systematic review which follows in Chapter 3. This literature review serves as both a conceptual framework for the research study and a primer for the reader. The main themes that are reviewed are substance dependence, neuropsychological assessment and executive functions.

### **2.2 Substance Dependence and Addiction**

#### **2.2.1 Introduction**

Various terminologies, models and theories are used in the field of substance dependence and addiction. These are delineated as a precursor for the study to ensure ambiguity is minimised. The historical development and different aetiological theories of addiction and substance dependence are presented. The behavioural neuroscience of substance dependence is outlined by discussing the primary neurochemical effects of psychoactive substances, the secondary effect of progression to addiction and exploring contemporary models informing current addiction research.

#### **2.2.2 History**

The concept of addiction has a documented history dating back 12 000 years, and before modern medical science the prevalent view of addiction was that of a moral transgression. In modern science there has been an evident evolution in the concept of addiction in the last couple of decades and by comparing the different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) this progression becomes clear (Nathan et al., 2016). The first two editions of the DSM, the DSM-I of 1952 and the DSM-II of 1968, deemed addiction as a societally disapproved disorder that primarily stems from personality disorders and, therefore, could be viewed as manifestations of underlying primary psychopathology (Robinson & Adinoff, 2016). The physiological symptoms of tolerance or withdrawal were only added to the DSM-III in 1980 as criteria for a diagnosis of substance dependence. Additional physiological and behavioural symptoms were included in both the DSM-III-R in 1987 and the DSM-IV in 1994. The



latest version, the DSM-5, provides numerous aetiological and symptomatic descriptions and emphasises the activation of the brain reward system with the use of psychoactive substances (American Psychiatric Association, 2013).

### **2.2.3 Conceptual Issues**

West, Marsden and Hastings (2019) stress that much fragmentation remains within the theoretical domain of addiction. This is evident in the lack of clarity over many constructs and the ambiguous ways of representing and understanding phenomena within the theoretical scope, as well as what constitutes to fall within this scope. Furthermore, ambiguous terminologies are used to describe models and theories in incongruent ways. Terms are used without clear definitions and at other times different terms are used for the same construct (West, 2001). The way in which research is reported complicates interpretation and in some instances makes it impossible to know what was done or what was discovered. Attempts at evidence synthesis in this field have been laborious and inefficient because of this fragmentation (West et al., 2019). Therefore, it is necessary to clarify the meaning of the terms *addiction* and *substance dependence* as they are used in the current systematic review.

The American Society of Addiction Medicine (2018, para. 1) provides a definition of addiction which acknowledges the condition as a disease of the brain:

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

From this definition, and within the context of psychoactive substances, addiction is fundamentally a condition that develops following the use of a psychoactive substance (Koob & Volkow, 2016; Lewis, 2018; Turton & Lingford-Hughes, 2016). That is, the psychoactive substance has a neurochemical effect on the central nervous system which

then results in the condition of addiction (Scofield et al., 2016). For research purposes, this explicit distinction is of vital importance as addiction and substance-use are not synonymous. To illustrate, the use of a psychoactive substance has a primary, acute effect on the central nervous system (Camí et al., 2003) even though addiction may not have developed. Conversely, an individual who suffers from addiction may be abstinent with physiological withdrawal symptoms which include adverse effects on the central nervous system (World Health Organization, 2019). When conducting research, the distinction between primary effects in acute or chronic use or the secondary effects of addiction as a neuropathology should be clarified.

In terms of diagnostic criteria, the American Psychiatric Association (2013) uses the term *substance-use disorder* to refer to the recurrent use of one or more substances which causes clinically significant impairment. Severity is classified as mild, moderate or severe. Furthermore, the following types of substance-related disorders are distinguished: alcohol; cannabis; hallucinogen; inhalant; opioid; sedative, hypnotic or anxiolytic; stimulant; tobacco; and other/unknown. The World Health Organization (2019) uses the term *dependence syndrome* to designate a physiological, behavioural and cognitive phenomenon with a strong, often overpowering, recurrent desire to take a psychoactive substance. In line with the types identified by the American Psychiatric Association, the substance dependence types are listed by the World Health Organisation as follows: mental and behavioural disorders due to the use of alcohol; cannabinoids; hallucinogens; volatile solvents; opioids; sedative-hypnotics; stimulants (including caffeine); cocaine; tobacco; multiple drug use or other psychoactive substances. The term *substance dependence* is used in this systematic review for any form of addiction to psychoactive substances whether a substance-use disorder or a dependence syndrome.

#### **2.2.4 Theories of Substance Dependence**

There are a multitude of theories to explain the phenomenon of substance dependence and the underlying condition of addiction (West, 2001) and recently the importance of reducing fragmentation and clarifying constructs amongst these theories have been emphasised (West et al., 2019). The numerous theories of addiction do not fall within the scope of this systematic review; however, I will provide a brief outline by using the four main theoretical views, namely the moral, psychoanalytical, behavioural and biological theories.

The *moral theory* contends that addiction is the result of deficits in the ability to take responsibility or a lack of spiritual strength (Lewis, 2018; Marlatt et al., 1988). Even though this notion may seem outdated in terms of current scientific progress, organisations such as Alcoholics Anonymous and Narcotics Anonymous (Krentzman et al., 2010) rely on this view as a foundation for treatment and, typically, religious teachers or spiritual guides facilitate individuals to take the moral path of abstinence. The effectiveness of these treatment models remains controversial and a review by Kaskutas (2009) reported mixed results from experimental studies. In addition, a systematic review by Ferri et al. (2006, p. 2) found that “no experimental studies unequivocally demonstrated the effectiveness of AA [Alcoholics Anonymous] or TSF [Twelve Step Facilitation] approaches for reducing alcohol dependence or problems”.

The *psychoanalytical theory* is based on individual developmental differences. The traditional view states that substance dependence is caused by, amongst others, the developmental stasis at a significant stage of personality development, in other words, the oral phase. Contemporary psychoanalytic views include concepts such as self-soothing and the enactment of perverse fantasies (Hopper, 1996), addiction as an artificially induced drive (Bejerot, 1972) and addiction as a form of perversion (Keller, 1992). Yet another contemporary view explains the condition as compulsive attempts to reduce anxiety (known as a driving force in psychoanalytic theory) and to protect the self from debilitating and painful emotions (Gumbiner, 2010). The evidence for psychoanalytical interventions, as treatment for addiction, have generally been considered weak (Lo Coco et al., 2019; Vijayakrishnan & Verma, 2018). However, a recent meta-analysis reports that a combination of more than one form of therapy may be more effective (De Crescenzo et al., 2018) and another review found the effect sizes observed in various longitudinal studies were significant, which indicates that the effects of psychotherapy may be more evident in long-term follow up (Vijayakrishnan & Verma, 2018).

The *behavioural perspective* contends that substance dependence is persistent and repetitive learnt behaviour based on short-term rewards despite the long-term negative consequences of said behaviour (Marlatt et al., 1988). The powerful desire to continue the activity is within voluntary control. Because of tolerance, the frequency, duration and amount of activity increase over time. The individual develops a psychological and physiological dependence on the gratification derived from the activity which has the same fundamental process as any other learned behaviour (Lewis, 2017). Other related theories

include the loss-grief addiction model (Beechem et al., 1996), substance dependence as a compulsive behaviour (Koob et al., 1998), the learning models of addiction (Lewis, 2018; O'Brien et al., 1992), the self-administration paradigm (Jones & Comer, 2013) and cognitive-behavioural models (Tiffany, 1990). A systematic review investigating the effectiveness of cognitive behavioural therapies as treatment revealed that lowered substance use and other positive changes were observed (Lee & Rawson, 2008). In another systematic review, the use of behavioural therapy in substance use and depression reported some positive effects, however the heterogeneity of the included studies was high (Martínez-Vispo et al., 2018).

The *biological theory* explains addiction based on underlying biological factors and processes (West, 2001). The current systematic review is for the most part grounded in the biological theory as the included studies make use of neuropsychological theories and instruments to conduct research (see section 2.3). The levels of analysis used in biological models include general biochemical mechanisms (Betz et al., 2000), structural and/or functional systems (Schofield et al., 2016; Volkow & Fowler, 2000; Volkow et al., 2017; Yager et al., 2015), genetics and epigenetics (Long et al., 2015; Morozova et al., 2012; Pierce et al., 2018) and neuroplasticity (Gilpin & Roberto, 2012). Preclinical and clinical studies have demonstrated neuroplasticity (biochemical and functional brain changes) with repeated exposure to psychoactive substances (Sampedro-Piquero et al., 2019). This is the primary tenet of the brain disease model of addiction (see section 2.2.6) which explains substance dependence as a progressive condition characterised by neurobiological adaptations with the use of psychoactive substances (Koob et al., 2016).

Research based on the disease model has been beneficial in various ways. It has increased our understanding of the behavioural symptoms of substance dependence – such as loss of control, compulsive and inflexible behaviours and negative emotional states. It has also played a role in the discovery of specific molecular targets and circuits (see section 2.2.5) which have resulted in the development of new medications for treatment (Kalivas & Volkow, 2011). There are various pharmaceutical interventions available for substance dependence treatment, with some proven more effective than others. For example, naltrexone and acamprosate are used for alcohol dependence. A systematic review investigating the effectiveness of these pharmaceutical treatments found that both were effective for alcohol dependence treatment and especially as adjuvant therapies (Carmen et al., 2004). For opioid dependence, a Cochrane review by Mattick et al. (2014)

was conducted to investigate the effectiveness of buprenorphine maintenance versus morphine maintenance or placebo. This review found that buprenorphine may reduce opioid use effectively compared to placebo, but only at high doses. In addition, treatment retention is higher than placebo for individuals on any dose of buprenorphine. However, treatment retention was lower for individuals using buprenorphine than methadone. In addition to the development of medication, research based on this model has also informed and improved new techniques such as transcranial magnetic stimulation (a non-invasive magnetic stimulation of the brain which alters neural activity), as well as provided clinicians with a framework to guide behavioural interventions in treatment (Volkow & Koob, 2015).

### ***2.2.5 The Neurochemical Mechanisms of Psychoactive Substances***

Neuropsychological assessment entails making inferences about neurological mechanisms based on behavioural observations. At the most fundamental level, psychoactive substances alter synaptic transmission (signals within the central nervous system) which results in the observed physiological and behavioural effects. As a rule of thumb, these substances either facilitate or inhibit synaptic transmission. Substances can inhibit the effects of or block a neurotransmitter, in which case the substance is an antagonist; whereas if a substance increases the effects or mimics a neurotransmitter it is an agonist. The substance can also have a mixed effect as an agonist-antagonist – for example, agonist at some doses; antagonist at other doses. Furthermore, the varied effectiveness and side effects of psychoactive substances from one person to another can be attributed to the differences in the number, type and location of receptors between individuals (Kalat, 2016). The desirable effects of psychoactive substances on the central nervous system are the primary reason for initial use and the different classes of psychoactive substances have varied mechanisms of action which explain the unique experiences of each (Camí et al., 2003). These different mechanisms of actions would therefore also be of significance for the observed behaviour of participants in research. In addition to the unique mechanism of action of each class of substance, activation of the mesolimbic dopaminergic system is central to the use of all addictive psychoactive substances (Lüscher, 2016). In short, dopamine is released from the ventral tegmentum to the nucleus accumbens which results in experiences of euphoric states or relief of distress and, thereby, reinforcing the behaviour (Camí et al., 2003). Curiously, the latter has not

been observed with benzodiazepine (Turton & Lingford-Hughes, 2016); however, this may be because of a lack of empirical research.

### **2.2.6 *Contemporary Models of Addiction***

Although there are various models to explain addiction, the brain disease model of addiction is internationally the primary accepted model (Lewis, 2018) and it is now widely accepted that addiction is a chronic, relapsing brain disease which can be explained by neurofunctional impairments (American Psychiatric Association, 2013; American Society of Addiction Medicine, 2018; National Institute of Drug Abuse, 2014). The brain disease model has nonetheless been challenged within the addiction field (Gruenert, 2010; Kalant, 2010; Satel & Lilienfeld, 2013) with the biggest alternative contender being the developmental learning model (Lewis, 2017, 2018).

Volkow et al. (2016) present the brain disease model of addiction and explain the phenomenon as progressive neuroadaptations with reoccurring stages that present with specific behavioural and clinical characteristics. These stages are (1) binge and intoxication, (2) withdrawal and negative affect and (3) preoccupation and anticipation. As the respective stages reoccur, neuroadaptations are reinforced, and the severity of the addictive process increases, hence the progressive nature of the condition. These progressive neuroadaptations which manifest from initial experimental use to the transition to addiction can be explained by changes in biochemistry (Camí et al., 2003; Koob & Simon, 2009; Turton & Lingford-Hughes, 2016), genetics (Demers et al., 2014; Volkow & Muenke, 2012) and functional neurocircuitry (Berridge & Robinson, 2016; Everitt & Robbins, 2013; Goldstein & Volkow, 2002). During the binge and intoxication stage, reward regions in the brain are activated by means of a high release of dopamine. Subsequently, this triggers associative learning and the reward is paired with the environmental stimuli preceding this reward (Wise, 2008). With repeated exposure to the reward, dopamine is released in an anticipatory response to the environmental stimuli, in other words, the cues (Schultz, 2002). With manifested addiction, the reward and motivational systems adapt through associative learning to focus more on the potent release of dopamine when the reward and cues are present – withdrawal and negative affect, the second stage, is experienced until satiation is achieved (Berridge & Robinson, 2016). Another important feature of this stage is that normal day-to-day conditions lose motivational weight. In other words, any activities or situations that provided pleasure to

the individual before are no longer pleasurable and progressively social, familial, and occupational domains are affected. Even more, continued exposure gradually lowers the sensitivity of the reward system to stimulation from the new reward and results in a desensitization of both substance-related and non-substance-related rewards gradually develops (Hägele et al., 2015). In conjunction, withdrawal sensations and the associated negative affect intensify gradually with these progressive neuroadaptations (Koob et al., 2016). Finally, within the preoccupation and anticipation stage, prefrontal brain regions and associated circuits are compromised with the continuous down-regulation of dopamine signalling. Self-regulation, decision making, flexibility in the selection and initiation of action, attribution of salience and monitoring of error are affected (Goldstein & Volkow, 2011) and results in behavioural impairments. These are all constructs of executive functioning, further supporting the relevance of the current systematic review.

The opposing developmental learning model acknowledges the neuroadaptations of the brain disease model but strongly rejects the ethos of the brain disease model and places emphasis on addiction as learned and habitual behavioural patterns. (Hall et al., 2017; Lewis, 2017). In short, the repetition of experiences modifies synaptic networks. This, in turn, creates a feedback cycle between experiences and brain changes. The brain changes that result from repeated learning experiences naturally settle into neural and cognitive habits (Lewis, 2018). Furthermore, the experiences that are repeated most often are those that are most compelling. Intense, recurrent desires change the speed and depth of learning by augmenting the reciprocal cycle between experiences and changes in synaptic networks. In sum, the developmental learning model emphasises that addiction is an outcome of natural learning which is accelerated and strengthened by the recurrent pursuit of attractive goals (Lewis, 2017, 2018). The latter refers to executive functioning and once again supports the importance of the current systematic review. Even though the two models disagree on the definition of addiction, both models agree on the various aetiological factors contributing to the development of addiction and the consequent neuroadaptations on various levels of analysis.

## **2.3 Neuropsychological Assessment**

### **2.3.1 Introduction**

In this section, neuropsychological assessment as a subfield of psychometry is discussed. Important psychometric properties of assessment are described, which include

the different reliability and validity types, the conventional procedures to conduct assessment and the importance of cultural sensitivity. Lastly, the domains of interest for neuropsychological assessment are presented using an integrative conceptual framework.

### ***2.3.2 Definition and Overview of Neuropsychological Assessment***

Lezak et al. (2012) define neuropsychological assessment as the quantitative, standardised measurement of the most complex aspects of human behaviour – the mental faculties of cognition, executive functions and emotional processing. As with any psychological assessment practice, specific domains of functioning are sampled by neuropsychological assessment instruments and, from these, inferences can be made about normal and atypical functioning (Harvey, 2012; Lezak et al., 2012; Morgan & Ricker, 2017; Schoenberg & Scott, 2011).

The practice of psychological assessment, in general, has several characteristics and these are also central to the subfield of neuropsychological assessment. As outlined by Foxcroft and Roodt (2013), many different procedures are used in various contexts and for different populations. These factors determine both the appropriate selection of assessment instruments, the administration of the measure, and the interpretation of the obtained results. Administering the instruments takes place under controlled conditions and systematic methods are used to evaluate assessment protocols. Thereafter, specific guidelines are used to interpret the results of assessment and scores can either be compared to that of an appropriate norm group or to a predefined criterion. Scores can also be used for qualitative classification purposes such as personality traits or diagnostic categories. Furthermore, instruments are developed in a specific context and for a specific purpose and this should always be borne in mind when interpreting scores. Specifically, the normative information that is used for interpretation is limited to the characteristics of the normative sample. It is important that assessment instruments are supported by evidence of reliability and validity for the intended purpose of use. This evidence is typically available in a technical test manual based on appropriate theory and research, but is also supplemented by findings from empirical studies that were conducted after publication of the instrument.

Reliability refers to the consistency of measurement and varies with sample characteristics (Heale & Twycross, 2015). Ideally, reliability coefficients are determined by gathering data from both healthy individuals and clinical populations (Morgan &



Ricker, 2017). There are different types of reliability evidence to consider for neuropsychological assessment scores. *Internal reliability* reflects the degree to which single items within an instrument measure the same construct. To illustrate, if the internal reliability coefficient of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) working memory index is  $r = 0.94$ , the working memory score obtained from administration of this measure has a high reliability in terms of the items within the measure that all measure working memory (Sherman et al., 2011). *Test-retest reliability* provides the correlation between scores of the same instrument administered on two different occasions. It is also called a coefficient of stability. A high test-retest reliability coefficient indicates that the score will show little change over time. The test-retest coefficient is influenced by the time interval between two administrations. There is no standard for this interval and it can vary from one instrument to another. When an instrument needs to be administered more than once, however, the confounding effects of practice need to be considered (Sherman et al., 2011). *Alternate forms* are administered to account for this, and the correlation between the different forms is called the coefficient of equivalence. However, with alternate forms, it is possible to introduce content sampling error and time sampling error. Instruments with alternate forms require rigorous psychometric standards to avoid introducing these sources of error. This includes very high correlations between forms, and very high test-retest reliability for both forms with equivalence in terms of mean scores and consistency in score classification. Many instruments are administered and scored in a straightforward right or wrong manner (Sherman et al., 2011). However, there are tests that have a subjective component with the potential for scorer variance. *Interrater reliability* refers to the degree of consensus between different scorers of assessment instruments. Test manuals provide specific and detailed instructions for the administration and scoring of instruments to avoid introducing errors based on scorer differences (Heale & Twycross, 2015). Assessment scores can be interpreted as possessing different types and degrees of reliability. How a test score is used, the purpose and with whom determine the importance of consideration of the different types of reliability (Lezak et al., 2012; Strauss, et al., 2006). For example, the scores obtained from a demanding decision-making assessment may have high reliability in normal-functioning individuals but have low reliability in individuals with physiological withdrawal.

Validity refers to what construct an instrument measures and to what degree it measures this construct (Heale & Twycross, 2015). Validity is related to scores in terms of the purpose of the instrument. Content-related validity, construct-related validity and criterion-related validity are the three validity types described by Strauss et al. (2006). *Content-related validity* involves whether or not the content of the assessment instrument covers a representative sample of the domain to be measured. This is typically determined by evaluating if an adequate description of the theoretical model is provided; a review of the literature is available; a definition of the domain of interest is provided together with a operationalisation of the definition (a thorough and systematic review of the domain); and the collection of a sample of items (adequately large to be representative of the domain with a sufficient range of difficulty) (Sherman et al., 2011). *Construct-related validity* is the extent to which the assessment instrument measures the intended theoretical constructs. Some of the factors to critically evaluate the construct-related validity of neuropsychological instruments include whether the constructs are formally defined; a measurement hypothesis is provided; the constructs have been validated through empirical evidence; the sensitivity of the instrument has been demonstrated; results have been correlated with other instruments; studies of group differences have been conducted; factor analytical studies have been conducted; and the level of internal consistency (Heale & Twycross, 2015). *Criterion-related validity* is the correlation coefficient between a criterion and predictors. This includes concurrent validity which is the accuracy of identification or diagnosis of current behaviour or status and predictive validity which is the accuracy of predicting future behaviour or category status (Sherman et al., 2011). Some of the factors to critically evaluate the criterion-related validity of neuropsychological instruments are the appropriate identification of the criterion; the appropriate identification of the sample group which reflects the population of interest; and the analysis of instrument-criterion relationships which include using contrasting groups, correlations with other instruments, accuracy statistics of positive predictive power, outcome studies and meta-analysis (Strauss et al., 2006).

Neuropsychological assessment typically follows a sequential process of instrument selection, administration and the interpretation of results. In terms of instrument selection, a multitude of neuropsychological instruments and batteries are available for use (Strauss et al., 2006) and adequately framed questions must be formulated to inform instrument selection. The technical aspects of the instrument, as outlined in the test

manual, should be scrutinized to determine if the instrument will be reliable and valid for the intended purpose (Lezak et al., 2012). The administration of an instrument is standardised and done in a controlled setting. The test manual provides the required protocols to follow and the assessor is responsible to ensure these protocols are adhered to. If administration is not done as prescribed the obtained score cannot be used for interpretation (Strauss et al., 2006). Finally, the interpretation of results can be done in various ways as described by Foxcroft and Roodt (2013). *Descriptive interpretation* refers to functioning as is at the time of administration, based on currently available information. This form of interpretation is only valid if the conditions of construct, content and concurrent validity are met. *Causal interpretation* describes the effects of specific conditions or events on functioning based on assessment results. A descriptive interpretation will precede a causal interpretation and information from empirical evidence, such as studies with standardised samples, can be used to determine validity. Confounding variables and task impurity are important factors to consider with causal interpretations. *Predictive interpretation* relies on the relation between current functioning, as determined by assessment results, and a future criterion. This form of interpretation is subject to the predictive validity of the instrument. Lastly, *evaluative interpretation* is a combination of the interpretation of the assessment results with a value judgement. In applied contexts such as counselling and treatment settings evaluative interpretations are often used and recommendations are made which can only be justified by validity data (Foxcroft & Roodt, 2013).

Various populations, contexts and assessment instruments are included the current systematic review. Therefore, the reliability, validity and neuropsychological assessment procedures are important considerations for the quality assessment of the included studies.

### **2.3.3 Cultural Sensitivity**

The current systematic review is predicted to include studies from numerous international countries and cultures. Therefore, another important consideration for neuropsychological assessment is cultural sensitivity. The differences or similarities observed in test scores of performance between individuals from different cultural or language groups need to be valid. Therefore, it is important for assessment instruments to be equivalent in terms of the individuals having the same or similar standing on the measured constructs (Foxcroft & Roodt, 2013). For example, individuals with high

working memory skills but different spoken languages should obtain the same or similar scores on the different language versions of an assessment instrument for working memory.

Considering the broader impact of cultural-sensitivity in neuropsychological assessment, Greenfield (1997) emphasises that assessment instruments are implicitly based on assumptions about values, knowledge and communication. If instruments are used on individuals from a culture that have different values, knowledge and communication than that which the instruments assume, the validity of the assessment is undermined. Ardila (2005) builds on this view by presenting specific culturally-determined aspects that are important to consider with neuropsychological assessment. He explains the unique way an individual relates to other people and persons from outside their culture is determined by cultural values. Moreover, the emphasis and specifics of background authority differ from one culture to another. For example, in a typical neuropsychological assessment situation, the test administrator is required to give instructions to the test subject and the test subject is expected to carry out (follow or obey) these instructions. Intuitively, behaviour will be influenced by the role the test taker assumes and, in this way, performance scores may be affected by culturally based realities about authority (Wong & Fujii, 2004). The notion of *best performance* also differs from one culture to another. Specifically, a culture that is highly competitive will have a different value attached to what is considered best performance than a less competitive culture (Ardila, 2005). Robertson et al. (2009) explains this with the observation that some cultures may consider thoughtful, cautious and deliberate actions as best performance, whereas other cultures may place an emphasis on accuracy at the highest possible speed for best performance. This is also closely related to the subjective experience of time and speed, which varies significantly across different cultures (Ardila, 2005). Neuropsychological assessment instruments with performance scores based on the speed of completing a task, for example the Trail-Making Test, may be influenced by this cultural value (Agranovich et al., 2011). Furthermore, the assessment environment and acceptable standards of this environment should also be considered. For example, in some cultures the private assessment environment, with the test taker and administrator in an isolated room, may be inappropriate (Ardila, 2005). In terms of communication, this goes beyond verbal language and special types of communication are uniquely determined by culture and cultural settings. The latter will have a significant impact on the validity of assessment that rely heavily on the use of formal verbal language

(Ardila, 2005). Finally, the knowledge dimension of culture has an impact on neuropsychological assessment because the process of knowing and the object of knowledge is culturally dependent (Greenfield, 1997). For instance, familiarity differs considerably between cultures for physical elements such as figures, objects, blocks and pictures (Rosselli & Ardila, 2003). This, once again demonstrates the importance of equivalence.

#### **2.3.4 Neuropsychological Domains**

The current systematic review will include studies using a myriad of neuropsychological assessment instruments and these instruments, in turn, measure various neuropsychological domains. As mentioned in the previous section, the specific domains of functioning are sampled to make inferences about normal and atypical functioning (Schoenberg & Scott, 2011). These domains are based on three functional systems according to Lezak et al. (2012), namely cognitive functions, emotionality and executive functions.

For heuristic purposes, I first present the perception-action cycle to conceptualise the operation of the functional systems and to further demonstrate how these systems are integrated. In short, Fuster (2004, 2017) describes this neurofunctional framework as the flow of information from the environment (either the external environment or internal feedback) to sensory structures (posterior cortex); then, from sensory structures to motor structures (anterior cortex), and back again to the environment, continuously updating in a circular fashion. The flow of information and formation of memory occurs hierarchically along the cerebral cortex. The highest level of this hierarchy is the prefrontal cortex implicated in complex schemas and plans of goal directed action which require temporal integration and organisation of behaviour (Fuster, 2004, 2017).

In terms of the cognitive functions, Lezak et al. (2012) provide a description of four constituent sub-domains, namely: receptive functions, memory, thinking and expressive functions. (1) *Receptive functions* are the selection, acquisition, classification and integration of information. This includes sensory processes and perception. (2) *Memory and learning* pertain to the storage and retrieval of information (for which the receptive functions are a prerequisite). (3) *Thinking* overlaps with executive functions; however, thinking is a narrower construct defined as the organization and reorganisation of information. Lastly, (4) *expressive functions* are the direct observable behaviours such as

speaking, writing, drawing, manipulation, gesturing and facial movements. Mental activities are explained by making inferences about expressive functions. In essence, the four sub-domains of cognition answer the general questions of *How much?* and *What?*, for example: “How much do you know?” and “What can you do?” (Lezak et al., 2012).

The functions of emotionality include the domains of emotions, mood, volition and motivation. Historically, the construct *emotion* has been difficult to define; however, in a general sense, the term is used for any of several subjectively experienced states (Reber & Reber, 2001). With a more precise view, affective neuroscience defines emotion as the ability to subjectively experience certain states of the central nervous system (Panksepp, 2004). In addition, the motivation to act on any behaviour is determined by emotional weight and, subsequently, this determines volition. *Volition* is the capacity for intentional behaviour through the process of determining what is needed or wanted and cognitively conceptualising a future realization. It, therefore, requires the capacity to formulate a goal; and apathy, with diminished or even absent capacity for emotional response, is typical in volitional impairment (Lezak et al., 2012).

Executive functioning is the third functional system and can be described as purposive, future-oriented or goal-oriented behaviours (Goldberg, 2017). As executive functioning is central to the current systematic review a detailed discussion is provided in section 2.4.

On a final note, the variables of mental activity are the level of consciousness, arousal and alertness; attentional functions; and activity rate (or speed of processing). In short, these variables constitute the efficiency of the functional systems (Lezak et al., 2012) and although the variables of mental activity are not specific domains, these variables are important when conducting neuropsychological assessment.

## **2.4 Executive Functions**

### **2.4.1 Introduction**

In this section, a number of definitions as well as the historical development of executive functions as a scientific construct are discussed in terms of the most prominent theories available. Thereafter, the various subcomponents of executive functions are delineated and contextualised and the brain-behaviour relationship of executive functions is presented based on available neuropsychological and neuroimaging research. The

prominent neuropsychological assessment instruments used to measure executive functions is outlined and some of the major measurement issues are presented. The section concludes with a discussion on the importance and relevance of executive functioning.

#### **2.4.2 Definition and Description of Executive Functioning**

In a comprehensive review, Jurado and Rosselli (2007) describe executive functioning as enabling the individual to shift mental attention for adaptive responses, while simultaneously inhibiting inappropriate behaviours, within a constantly changing environment. Furthermore, executive functions allow the individual to formulate future-oriented, goal-directed plans, initiate execution and persevere until completion. The *Encyclopedia of Clinical Neuropsychology* (Stern et al., 2017) describes executive functioning as a multifaceted construct. It encompasses a collection of sophisticated mental abilities underlying independent goal-directed behaviours, problem-solving and the efficiency of knowledge accumulation. Therefore, this broad construct includes abilities such as initiation, planning, organising, working memory, attention, mental flexibility, inhibition, emotional regulation and self-monitoring. Lezak (2012) describes executive functioning as the successful engagement in independent, purposive, self-directed and self-serving behaviours by an individual and includes the domains of planning, decision making, purposive action, volition and effective performance. Executive dysfunction, even to a lesser extent, is directly correlated to impairment in basic day-to-day functioning (Lezak et al., 2012).

#### **2.4.3 Models of Executive Functioning**

Various models and theories of executive functioning have been developed and, notably, these complement each other. The models may differ in the level and scope of analysis but at the same time, when considered collectively, complete a greater picture of this highly complex construct. I briefly discuss the most prominent models of executive functioning and present the central tenet of each model in Table 2.1.

In 1973 Alexander Luria published *The Working Brain: An Introduction to Neuropsychology*. At the time, he proposed that the human brain is comprised of three basic functional units. The brain stem maintains arousal of the cortex; the parietal, temporal and occipital lobes are responsible for the encoding, processing and storage of information; and the programming, regulation and verification of behaviour occur within the frontal lobes (Chan et al., 2008). It was only in 1974, however, that the construct

*executive function* originated from the central executive component of Baddeley and Hitch's working memory model (Jurado & Rosselli, 2007). Baddeley and Hitch (1974) proposed that working memory is made up of different components: the visuospatial sketchpad, the phonological loop, the central executive and the episodic buffer. The visuospatial sketchpad retains visual and spatial information for a brief period. The sketchpad contains two distinct components: The first component retains information for specific features of an object and the second component retains sequential spatial information. The phonological loop holds inner speech for a brief period, and can be further divided according to the functions of phonological storage and subvocal rehearsal. The central executive coordinates activities of attention and governs responses. In conjunction, the episodic buffer integrates information between the visuospatial sketchpad, the phonological loop and long-term memory (Sternberg & Sternberg, 2012).

In 1983, Lezak defined the construct of executive function as the dimension of human behaviour that deals with "how" behaviour is expressed (Jurado & Rosselli, 2007). Specifically, the delineated sub-domains of volition, planning, purposive action and effective performance can be evaluated by observing expressive behaviours linked to these domains and making appropriate inferences (Lezak et al., 2012). Around the same period, in 1986, Norman and Shallice introduced the supervisory attentional system model (Chan et al., 2008; Norman & Shallice, 1986). Building on Luria's notion of frontal lobe functioning, this model proposed that the programming, regulation and verification of human behaviours involve two systems. The first, the contention scheduling system is responsible for routine and overlearned behaviours and the order of these behaviours are prioritised. The second, the supervisory attentional system, regulates non-routine and novel behaviours (Jurado & Rosselli, 2007). Norman and Shallice (1986) further proposed that situations which require the supervisory attentional system will include the following: (1) planning or decision-making; (2) troubleshooting or error correction; (3) responses containing unfamiliar or novel sequences of actions; (4) anticipated danger; (5) overriding a strong habitual response or resistance to temptation. Also in 1986, the tripartite model was introduced which comprises three interactional systems. The first two, the anterior reticular activating system and the diffuse thalamic projection system, primarily maintain arousal. The fronto-thalamic gating system is implicated in attention and executive functions (Chan et al., 2008). This model was expanded later and the *schema* was introduced which is a network of neurons activated by sensory input, other schemata, or



the executive control system (Stuss et al., 1995). On a neural level different attention and executive functions are identified: sustained attention correlates with the right frontal lobe; concentration with the cingulate area; divided attention with the cingulate area and orbitofrontal cortex; suppression with the dorsolateral prefrontal cortex; switching with the dorsolateral prefrontal cortex and medial frontal areas; preparation with the dorsolateral prefrontal cortex; and goal setting with the left dorsolateral prefrontal cortex (Chan et al., 2008).

It is well understood that emotion is also mediated in frontal regions. Marked emotional and social impairment is observed in ventromedial frontal cortex damage; particularly, the cortical links between ventromedial cortex and the subcortical links of mediodorsal nucleus of thalamus, amygdala and hypothalamus (Chan et al., 2008). Based on the latter, Damasio (1996) introduced the importance of emotions in relation to executive functioning. The somatic markers model is grounded in the findings that ventromedial damage impairs the ability to mark inappropriate behaviour with an emotion-related somatic signal even though the individual might be able to understand the implications of such behaviours. These individuals will show difficulties in regulating their behaviours because they could not make use of emotional-related somatic markers.

According to the goal-neglect theory (Duncan et al., 2008), human behaviour is goal-oriented and specific goals contain subordinate lists or sub-goals. Moreover, goals are formulated, stored and monitored in the mind for the individual to behave optimally in response to environmental and internal demands. One of the main functions of goals is to impose a structure on behaviour by determining the activation or inhibition of behaviour that either promotes or prevents task completion (Chan et al., 2008).

Miyake et al. (2000) found both unity and diversity are evident in executive functions. That is, different executive functions correlate with one another (unity) but also show separability (diversity). The three executive functions investigated in this model are updating, shifting and inhibition. Updating is defined as the continuous monitoring and rapid addition and/or deletion of working memory contents; shifting is flexible switching between tasks or mental sets; and, inhibition is the deliberate overriding of dominant responses (Miyake & Friedman, 2012). The authors of this model acknowledge executive functions other than the three used in the unity/diversity model and emphasise that the specific constructs used depend on the level of analysis. For example, planning as an

executive function is regarded as a higher-level construct which includes all three constructs of updating, shifting and inhibition. These three constructs can be further decomposed into lower-level subconstructs. For example, updating can be decomposed into monitoring, addition, active maintenance, and deletion (Miyake & Friedman, 2012).

Fuster (2017) provides a comprehensive explanation of executive functioning using the perception-action cycle as a neurofunctional framework. This cycle is the circular processing of information with the aim being the adaptation of the organism to its environment. The prefrontal cortex plays a crucial role in the temporal organisation of behaviour and language by the preadaptation of the organism to internal or external events before they happen (Fuster, 2004). This can be regarded as a functional description of executive functioning which includes three major executive functions. The three major executive functions are executive attention, working memory and decision making. Executive attention, or attentional set, is the priming of sensory and motor systems for an anticipated and predictable adaptive response to a stimulus. Working memory is the temporary retention and manipulation of information for executing an action (performing a task or solving a problem) in the near future. Purpose and intentionality differentiate working memory from other forms of short-term memory. Decision making involves an intentional choice of prospective action among various alternatives. All three of these functions have a future-oriented purpose (Fuster, 2017). The central tenets of each of these various models of executive functioning are summarised in Table 2.1.

**Table 2.1**

*Models of Executive Functioning*

<b>Model</b>	<b>Central tenet of executive functioning</b>
Luria's working brain	The programming, regulation and verification of behaviour occur within the frontal lobes.
Baddeley and Hitch's working memory	The central executive coordinates activities of attention and governs responses.
Lezak's expression of behaviour	Sub-domains of volition, planning, purposive action and effective performance constitute executive functioning.
Norman and Shallice supervisory attentional system	Non-routine and novel behaviours are regulated by a supervisory attentional system.

Stuss and Benson tripartite model	The neurophysiological fronto-thalamic gating system is implicated in attention and executive functions.
Damasio's somatic markers	Behaviour is marked with an emotion-related somatic signal with direct implications for executive functioning.
Duncan's goal-neglect theory	Goals are formulated, stored and monitored in the mind for the individual to behave optimally in response to environmental and internal demands.
Miyake and Friedman's unity/diversity model	Different executive functions correlate with one another (unity) but also show separability (diversity).
Fuster's perception/action cycle	The prefrontal cortex plays a crucial role in the temporal organisation of behaviour and language by the preadaptation of the organism to internal or external events before they happen.

In conclusion, it is evident that the various models differ in the level of analysis and specific definitions; however, Jurado and Rosselli (2007) note that despite these differences, an agreement exists in the complexity and significant importance of executive functions for human adaptive behaviour. Nonetheless, until a consensus is reached, the use of these various models also necessitates that research studies should specify the level and scope of analyses when investigating executive functioning.

#### ***2.4.4 Current Understanding of the Neurophysiology of Executive Functions***

Thus far, the executive functions have been explained based on various theoretical models. However, because neuropsychology is grounded in the neurological basis of behaviour it is necessary to outline the current understanding of the neurophysiology of this construct. Historically, with the modular view of the brain, it was believed that executive functioning is narrowly associated with the frontal cortex. However, with advances in neuroscience, research suggests that executive functioning can be explained by a number of neural networks and areas of the brain (Stern et al., 2017). Based on human lesion and neuroimaging studies, prefrontal areas with respective connections to striatal and limbic regions, are linked to specific executive functions (Verdejo-Garcia, 2017). Specifically, the sub-domains of working memory is associated with the dorsolateral prefrontal cortex (Bogdanov & Schwabe, 2016); decision making with the medial

orbitofrontal cortex (Bechara, 2000; Rolls & Grabenhorst, 2008); response inhibition with the inferior frontal gyrus (Aron et al., 2014); and cognitive flexibility with the ventrolateral prefrontal cortex (Hampshire et al., 2008). The neurophysiology of executive functioning is highly relevant to the development of substance dependence and addiction and discussed in section 2.5. Furthermore, there is a bidirectional relationship between neuropsychological assessment and our understanding of the neurophysiology of the executive functions because these inform one another.

#### **2.4.5 Assessment of Executive Functions**

To recap, executive functions can be psychometrically distinguished from cognitive functions. Assessment of executive functions is based on *how* or *whether* a person presents behaviour, whereas the assessment of cognitive functions involves *what* or *how much* a person presents behaviour (Lezak et al., 2012). Although executive functioning is regarded as one of the most complex human activities, there are several measurement techniques available to allow for the observation of behaviours associated with underlying executive functions. The main techniques are neuropsychological assessment, neuroimaging (such as computerised tomography) and neurofunctional assessment (for example, functional magnetic resonance imaging). For the purpose of the current systematic review, only neuropsychological assessment is discussed.

There are many neuropsychological instruments and batteries used to measure executive functioning. The most prominent of these, as depicted by Lezak et al. (2012) and Strauss et al. (2006), are the Wisconsin Card Sorting Test, the Stroop Test, the Trail Making Test, the Controlled Oral Word Association Test, the Hayling Sentence Completion Test, the Brixton Spatial Awareness Test, the Tower of London and the Tower of Hanoi. The *Wisconsin Card Sorting Test* assesses shifting, maintenance, and inhibition of the cognitive functions of rule detection and concept formation. Four stimulus cards are placed in front of the subject. The objects printed on the cards vary in shape, colour and number. The subject is given a deck of similar cards and instructed to arrange the cards under the stimulus cards according to an unknown rule that changes after every six placements without warning (Jurado & Rosselli, 2007; Lezak et al., 2012; Strauss et al., 2006). The *Stroop Test* assesses inhibition, but also processing speed as a mental activity variable. The subject is required to read a list of colour words printed in black ink as fast as possible while being timed. Thereafter, the colour of a list of X's should be named as fast

as possible while being timed. Finally, the printed colour of a list of words should be named as fast as possible, ignoring the incongruent colour words. For example, if the word *BLUE* is printed in green ink, the subject is required to say “green” and inhibit the prepotent response (more powerful impulse) of saying “blue” (Jurado & Rosselli, 2007; Lezak et al., 2012). The *Trail Making Test* is comprised of two parts and measures shifting and inhibition. In the first part the subject is required to connect a sequence of encircled numbers with a pencil, as fast as possible. In the second part the subject is required to connect a sequence of encircled numbers but alternating between two different circle colours – inhibiting the prepotent response to connect the same coloured circles which are also printed on the page (Jurado & Rosselli, 2007; Lezak et al., 2012; Strauss et al., 2006). The *Controlled Oral Word Association Test* is a verbal fluency test and measures inhibition. The subject is instructed to name as many words as possible beginning with the letter *F*; thereafter the same instruction is given for the letter *A* and then the letter *S*. However, proper nouns, repeated words, colours and derivatives of the same word stem are not allowed (Jurado & Rosselli, 2007; Lezak et al., 2012; Strauss et al., 2006). The *Hayling Sentence Completion Test* has two parts. The subject is required to complete sentences with the last word missing. For the first part the word should make sense; however, the second part requires a word that does not match the context of the sentence – thereby requiring inhibition of the sensible response (Jurado & Rosselli, 2007; Strauss et al., 2006). The *Brixton Spatial Awareness Test* requires the subject to predict the position of a coloured circle from one page to the next. The subject does not know the rules. This assesses rule detection which includes updating and working memory maintenance (Jurado & Rosselli, 2007; Strauss et al., 2006). The *Tower of London* is a puzzle assessing decision making, planning and inhibition. The subject must determine the order of moves required to rearrange several rings to a new predefined arrangement. Only one ring may be moved to any of the two alternative pegs until the rings are rearranged as required (Jurado & Rosselli, 2007; Lezak et al., 2012). The *Tower of Hanoi* is a more difficult version of the Tower of London. Using the same rules, these rings are of different sizes and the subject is further required to order the rings according to size.

As with any scientific measurement, there are certain limitations to consider. The task-impurity problem is one of the primary caveats of executive function assessment. Task-impurity is a systematic non-executive function variance and measurement error which makes it difficult to accurately measure the executive function variance of interest

(Miyake & Friedman, 2012). For example, the Wisconsin Card Sorting Test discussed above includes systematic variance attributable to non-executive function processes, such as colour and form processing, sensory-motor functions and visuospatial abilities. In order to minimise this problem, the latent-variable approach can be used. In this approach multiple exemplar instruments are selected. The tasks of these instruments seem different at face value but capture the target ability. Multivariate statistical techniques such as confirmatory factor analysis and structural equation modelling can then be used to extract what is common across the different tasks (Miyake & Friedman, 2012). Other limitations include the possibility of assessment measures not being culturally sensitive, a shortage of normative data for specific populations being assessed and the estimation of premorbid functioning (Lezak et al., 2012).

#### ***2.4.6 Relevance of Executive Functions***

Lezak et al. (2012) explain that considerable loss of cognitive functions with intact executive functions allows the individual to continue to be independent, purposive, self-directed and self-serving. However, the loss of executive functions, even to a small extent, can cause impairment in these capabilities and present as problems with self-care, independent work and social relationships – regardless of preserved cognitive functions. It is clear, therefore, that executive functioning is fundamental to every aspect of human functioning. As explained by Diamond (2013), research has demonstrated how executive functioning is relevant to various aspects of life, including mental health (Malloy-Diniz et al., 2017), physical health (Mora-Gonzalez et al., 2019), educational performance (Gordon et al., 2018), job performance (Culbertson et al., 2013), quality of life (Love et al., 2016; Stern et al., 2017) and even public safety (Meijers et al., 2017; Seruca & Silva, 2016). In terms of substance dependence, executive function impairment is central to relapse and continued use through the loss of control over cravings and increased impulsivity. Specifically, the impairment of decision making, self-regulation, inhibition and working memory are directly linked to excessive salience attribution for substance-related cues and decreased abilities to inhibit maladaptive behaviours (Goldstein & Volkow, 2011; Koob & Volkow, 2016). The relevance of executive functioning in substance dependence, with reference to the specific substances, is discussed in detail in section 2.5.

## **2.5 Substance Dependence and Executive Functions**

### **2.5.1 Introduction**

The bidirectional manifestation of executive function impairment and addiction, as posited by the brain disease model, is explained in section 2.2.6. The focus in this section is the substance-specific effects on executive functioning and related neuropsychological domains based on existing research. The most comprehensive review of its kind (Fernández-Serrano et al., 2011) investigated the effects of cannabis, cocaine, methamphetamine, MDMA (ecstasy), opioids and alcohol on neuropsychological performance. In general, matched healthy control groups were used as comparators in the included studies of this review with one longitudinal study controlling for premorbid functioning by means of multiple assessment intervals. The study reports that even with the use or abuse of a primary substance, in the majority of cases, more than one substance is used simultaneously. This makes it challenging to establish correlations between specific substances and neuropsychological performance. However, to account for this, the review included three different methodologies and found for all substances examined a significant effect on the neuropsychological domains of episodic memory, emotional processing, updating and decision making. With a higher reliability, correlations between specific substances and distinctive neuropsychological domains were discovered. These findings, together with results from other studies, are discussed below.

### **2.5.2 Alcohol and Executive Functions**

Alcohol dependence has been found to impair processing speed, abstract reasoning, inhibition, endurance, memory, learning and planning (Punzi, 2015). Moreover, impaired spatial processing, reduced perceptual speed, selective attention, cognitive inflexibility and increased impulsivity were found in a synthesis of empirical studies (Fernández-Serrano et al., 2011). A recent meta-analysis by Stephan et al. (2017) examined the effects of alcohol on specific subcomponents of executive functioning. The impact of alcohol abuse on planning, problem solving, and inhibition was found to be significant. In another meta-analysis Stavro et al. (2013) examined the cognitive impairment caused by alcohol dependence and the duration necessary for recovery from this impairment. Moderate effect sizes, determined by Cohen's  $d$ , for the domains of executive functioning were found for short-term (<30 days), intermediate-term and long-term (>365 days) abstinent participants. It is, however, possible that withdrawal may have had an impact on the performance of

individuals. Therefore, it is important to account for this confounding variable when interpreting the findings.

### **2.5.3 *Cannabis and Executive Functions***

With early onset and chronic use, the effects of cannabis on attention, memory and executive functioning are significant. Furthermore, the effects of cannabis may be prolonged as some persistent impairments may be diffuse and subtle. Emotional functioning may also be impaired as individuals present with emotional numbing and amotivation (Punzi, 2015). A review of empirical studies found impairments in prospective memory, processing speed and complex planning with cannabis use (Fernández-Serrano et al., 2011). In addition, a recent review of meta-analytic studies by Verdejo-Garcia (2017), concluded that chronic cannabis use correlates with impairment of decision making and complex planning. This review also reports on findings that individuals with early-onset use in adolescence and those with genetic predisposition (val/val genotype of the COMT gene; short/short genotype of the SLC6A4 gene) have further impairments of decision making, sustained attention, response inhibition and flexibility. Another recent systematic review on the acute and chronic effects of cannabinoids on cognition reported mixed findings for the chronic effects of cannabis on executive functions (Broyd et al., 2016). The evidence for recovery of functions with abstinence was both mixed and at times insufficient. The reviewers also reported on the high heterogeneity in both sample demographics, especially high variance in substance exposure, and the assessment of cognitive domains. The effects of organic and synthetic cannabinoids on executive functions were recently investigated by systematic reviewing of both pre-clinical and clinical studies (Cohen & Weinstein, 2018). Findings demonstrate an association between repeated consumption of cannabinoids and impairment of executive functions. High heterogeneity was found in the samples in terms of the type of drug, the dosage, the age of onset and the duration of use. An earlier meta-analysis investigated the residual effects of cannabis use after abstinence on neurocognitive performance (Schreiner & Dunn, 2012). In this meta-analysis rigorous inclusion criteria were used to ensure generalizability. The study found a small negative effect for the first 25 days of abstinence, which may be attributed to either residue cannabis or withdrawal effects. However, no evidence was found for enduring negative effects. It therefore appears that the empirical evidence regarding the impact of cannabis on executive functioning is somewhat mixed, with most



studies reporting impairment in specific domains; however, the effects of various confounders remain unclear.

#### **2.5.4 *Hallucinogens and Executive Functions***

A literature search was conducted and no systematic reviews were found that explicitly investigate the effects of the hallucinogens on executive functioning. However, a systematic review was found that report on some findings for neuropsychological functioning. dos Santos et al. (2016) synthesised empirical studies of the psychiatric symptoms, neuropsychological functioning, and neuroimaging of ayahuasca (a psychoactive brew originating in South America) and reported that certain positive effects were found. With acute use, ayahuasca was found to improve planning, inhibitory control and working memory impairment. Subacute and long-term use showed enhanced cognition and reduced impulsivity. The authors further report, however, that some methodological limitations were found in the studies and that replication is necessary.

In general, research is sparse that investigate the relationship between executive functions and dependence on hallucinogens such as ayahuasca, dimethyltryptamine (DMT), psilocybin, lysergic acid diethylamide (LSD), mescaline, dextromethorphan, ketamine, phencyclidine (PCP) and salvia divinorum. This may be because of the low prevalence in comparison to other substance classes. The United Nations Office on Drugs and Crime (2017) reports that the global average of people seeking substance-related treatment for hallucinogens is less than one per cent.

#### **2.5.5 *Inhalants and Executive Functions***

Among the inhalant substances containing aromatic hydrocarbons such as styrene, xylene, n-hexane and toluene, the latter has the highest potential for abuse. Glue, lacquer and spray paint are toluene-rich industrial products. Even though existing research is scarce, existing studies show chronic inhalation of toluene has significant neurobiological and neuropsychological impairment as reported in a review by Yücel, Takagi, Walterfang and Lubman (2008). The review further reports that the included studies had findings of impairments in processing speed, sustained attention, memory retrieval, language processing and general executive functioning.

### **2.5.6 *Opioids and Executive Functions***

Existing studies indicate that opioids impair spatial and visual memory, impulse control, attention, and overall executive functioning. The same impairments also present with individuals undergoing methadone treatment (Punzi, 2015). According to a review of meta-analytic studies, chronic opioid use is linked to significant impairment in working memory and decision making, specifically for heroin and methadone. Prescription opioid drugs have not shown any significance based on the available research (Verdejo-Garcia, 2017). Furthermore, studies investigating the effects of long term abstinence indicate impairment in updating and decision-making as possible persistent opioid-related effects (Fernández-Serrano et al., 2011).

### **2.5.7 *Sedatives, Hypnotics, Anxiolytics and Executive Functions***

A literature search was conducted and no systematic reviews were found which explicitly investigate the effects of the sedatives, hypnotics or anxiolytics on executive functioning. This is noteworthy, as this substance class accounts for four per cent of the global average of individuals seeking substance-related treatment (United Nations Office on Drugs and Crime, 2017) which is a significant proportion. After a comprehensive search of the literature, the current systematic review may reveal to what extent this substance class has been investigated in relation to executive functioning.

### **2.5.8 *Stimulants and Executive Functions***

Working memory, attention and general executive functions are impaired by stimulants (Jovanovski et al., 2005; Lundqvist, 2005; Punzi, 2015; Wunderli et al., 2017). In addition, stimulants have a considerable effect on emotional, motivational processes and the capacity to remember future intentions (Punzi, 2015). Spatial processing, perceptual speed, processing speed, selective attention and complex planning impairments have been reported with chronic MDMA (ecstasy) use (Fernández-Serrano et al., 2011). Concurrently, it is reported in a review of meta-analytical studies that chronic cocaine use correlates with significant impairment in working memory and high perseveration (from reward-related inflexibility). Response inhibition and decision making are also impaired; however, these may be premorbid deficits (Verdejo-Garcia, 2017). In the same review, chronic methamphetamine use is reported to be linked with deficits in various executive functioning domains but these are in isolated studies and robustness is questioned, prompting further research (Verdejo-Garcia, 2017). Studies investigating effects with long

term abstinence indicate impairment in updating, inhibition, cognitive flexibility and emotional processing as possible psychostimulant-related effects (Fernández-Serrano et al., 2011).

### **2.5.9 *Nicotine and Executive Functions***

There appears to be a relationship between nicotine dependence and executive functioning (Fernández-Serrano et al., 2011; Flaudias et al., 2016). However, no systematic review is available in the literature that report on empirical studies that investigate the effects of nicotine on neuropsychological performance. The current systematic review may provide an overview of the extent of the current available evidence with regard to the relationship between nicotine and executive functioning.

### **2.5.10 *Conclusion***

The effects of the various classes of substances on executive functioning and related neuropsychological domains were presented based on existing reviews. It is evident that confounding variables need to be considered when interpreting results. For example, where the effects of a substance on neuropsychological performance are investigated, withdrawal may also have an effect on the results. Furthermore, studies within reviews have mixed findings and predominantly because of high heterogeneity in terms of substance type, dosage and frequency, age of onset and duration of use. Existing empirical studies of the neuropsychological effects of certain substance classes have not been systematically reviewed. In terms of the specific scope, no systematic reviews were found for hallucinogens; sedatives, hypnotics and anxiolytics; and tobacco.

## **2.6 Conclusion**

In this chapter, I presented a theoretical review as a precursor to and conceptual framework for the systematic review which follows in Chapters 3 and 4. It is evident from the theoretical review that there are sophisticated empirically supported models of both substance dependence and executive functions, together with well-refined measurement techniques for assessing executive functions and other neuropsychological constructs. However, limited work appears to have been done in terms of evaluating and synthesizing the available empirical evidence regarding the relationship between substance dependence and executive functions. I address this gap in the following chapters.

## **Chapter 3: Research Methodology**

### **3.1 Introduction**

In this chapter I describe the general research approach adopted, as well as the specifics of how it was applied to the current study. Because systematic reviews are still relatively uncommon in psychology, I present the conceptual basics of systematic review methodology in some detail, together with a description of the techniques of applying it in practice.

### **3.2 Research Approach: Systematic Review**

#### ***3.2.1 Introduction***

In this section the theoretical basis of the systematic review as a research methodology is discussed. The methodology is presented in terms of its historical development, its distinctive methods and processes, the strengths and limitations of conducting a systematic review, aspects of methodological quality and, to conclude, a comparison of the different review types.

#### ***3.2.2 Definition and Description***

It is crucial for policymakers and professionals to keep up to date with advances in their fields. However, the amount of available research is increasing exponentially and makes it practically impossible to keep abreast of all information. Systematic review methodology alleviates this issue to some degree by synthesising large bodies of research. In this way, it can elucidate what works and what does not work in order for researchers and practitioners to allocate scarce resources most effectively (Higgins et al., 2019).

According to Boland et al., (2017), a systematic review is a rigorous literature review with the primary aim of providing evidence-based answers to research questions. This is done by locating, appraising and synthesising the best available evidence from the literature by means of methods designed to minimise bias. Furthermore, a systematic review follows stages that are well-defined and transparent. This ensures the legitimacy of the identification of available evidence. It also ensures accurate synthesis of the findings to provide relevant conclusions. These stages follow a logical course, but also inform one another throughout the process (Boland et al., 2017; Gough et al., 2012).

### **3.2.3 Historical Development**

The methodology of synthesising previously published research reports is not new. Even as early as 1753, James Lind conducted research into scurvy prevention by carefully specifying his search strategy and extracting relevant data from the available publications (Chalmers, 2003). However, the basic tenets of the methodology were only formally established by two individuals in the 1970s: In 1972, Archie Cochrane proposed that because healthcare resources are limited it is necessary to properly evaluate the clinical effectiveness of any form of healthcare before use. He regarded randomised controlled trials (RCTs) as the best available evidence for this purpose (Cochrane, 1972). Within the next few years, Gene Glass conducted research which resulted in the development of statistical techniques to combine the results of independent studies, known as *meta-analysis* (Glass, 1976).

Recognition grew internationally following the groundwork laid by these prominent researchers and in 1992 the Cochrane Collaboration was established. At the time of writing, the collaboration comprises of an international network with thousands of dedicated individuals in more than 130 countries who work together for well informed decisions about healthcare (The Cochrane Collaboration, 2019). The methodology has also expanded to other fields such as the Campbell Collaboration that was established in 2000 with reviews focussing on the effects of social interventions in areas such as education, crime and justice (Boland et al., 2017; Campbell Collaboration, 2019).

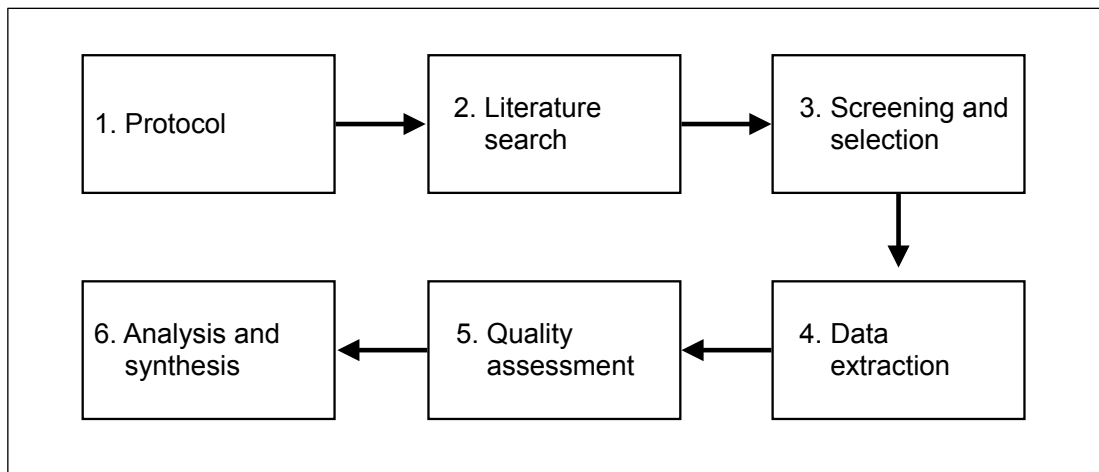
### **3.2.4 Essential Methods**

A systematic review follows a specific process that is well-defined and transparent. The stages of this process are illustrated in Figure 3.1. First, for a systematic review to adhere to the rigour and transparency of scientific inquiry, it is required to develop a detailed protocol. The protocol contains a clearly defined and well-focused research question and explicit, predefined methods for the literature search, screening and selection of studies, data extraction, quality assessment, data analysis and synthesis. Second, a literature search is conducted with an exhaustive list of key search terms which will ensure the highest probability of locating all relevant studies (Gough et al., 2012; Shea et al., 2017). Furthermore, the most appropriate databases should be selected based on the field of inquiry and at least two databases should be used to search for publications (Shea et al., 2017). Third, studies from the search results are screened and selected using clear

inclusion and exclusion criteria. These criteria are formulated in terms of various study characteristics (e.g., populations, study designs, etc.). The degree of specificity with which these criteria are defined is determined by the depth and breadth of inquiry required to answer the review questions.

**Figure 3.1**

*Stages of the Systematic Review*



Fourth, after the relevant studies have been selected the data are extracted from the included studies and tabulated. Fifth, quality assessment is conducted which can be done both prior to and after data extraction. The benefit of doing quality assessment after data extraction is that the reviewers are more familiar with the specific data and thereby better able to identify quality aspects of the studies. However, it is possible, where quality assessment is only done after data extraction, that unnecessary data extraction is done from studies that might have been excluded based on quality criteria. Important elements that are considered in the quality assessment of studies are discussed in section 3.2.6 of this chapter. Finally, the extracted data from the independent studies are then combined and analysed to describe and summarise the gathered information. This is known as a narrative synthesis and is a requirement of a systematic review. Systematic reviews that focus purely on quantitative findings often make use of statistical meta-analysis but this is only feasible for data with low heterogeneity at face value. Whether conducting a narrative synthesis or a meta-analysis, the findings of a systematic review allow adequate comparisons to be made and the identification of possible consensus or near-consensus findings and inconsistencies. It may also be possible to uncover gaps and exhaustive evidence in the available research.

### **3.2.5 *Strengths and Limitations***

Systematic review methodology is considered the gold standard to synthesise studies investigating the same problem or question. In the United Kingdom, systematic reviews form the basis of clinical practice based on the National Institute for Health and Care Excellence Guidelines (Boland et al., 2017). The World Health Organization also uses systematic reviews to formulate standard international guidelines. Any implemented guidelines are required to be supported by at least one systematic review of the evidence (World Health Organization, 2014).

There are various scientific benefits to using a systematic review as a research methodology. The methodology is explicitly reproducible as the protocol provides predefined methods that are followed which ensure that bias is minimised in the study. These methods include a systematic search and selection of studies based on predefined eligibility criteria and clear objectives. Included studies are quality assessed using tools specifically designed for this purpose and the findings are also synthesised and presented systematically. All of these features optimise the scientific rigour and transparency of the review. Furthermore, the findings of a systematic review are also used to advance the respective field of enquiry; informing future practice and research; and, when combined with professional judgement, informing interventions and policies (Perrier et al., 2011). Of utmost importance, the evidence from systematic reviews can be used to ensure that scarce resources are allocated more effectively (Higgins et al., 2019).

A systematic review has a specific scope and may be limited or strengthened by the depth and breadth of investigation (Gough et al., 2012). A narrow and in-depth review may be limited by excluding important confounding data which a broad and general review may include; in contrast, a broad and general review may be limited by failing to provide precise and explicit outcomes which a narrow, in-depth review may provide. This is explained in more detail in section 3.2.7 of this chapter.

### **3.2.6 *Methodological Quality***

The Assessment of Multiple Systematic Reviews Tool (AMSTAR) is commonly used to determine the methodological quality of systematic reviews (Pieper et al., 2018). The following criteria are applicable to the methodological quality of a narrative systematic review (Shea et al., 2017):

(1) The research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparator and Outcomes). This includes specifying, for example, the demographics of the participants used in the studies, the type of treatments administered, the comparator groups used (such as healthy control participants or participants receiving placebo treatments), and the type of outcome (such as treatment outcome or assessment outcomes). (2) The report of the review contains an explicit statement that the review methods were established prior to conducting the review and any significant deviations from the protocol are justified. (3) The selection of the particular study designs for inclusion in the review is appropriately justified. (4) A comprehensive and exhaustive literature search strategy is used. (5) Study screening and selection is performed in duplicate. This requires each reviewer to select articles independently and blinded to ensure bias is minimised. Blinded selection entails that the selection made by one reviewer should be unknown to the other reviewer. (6) Data extraction is performed in duplicate. Each reviewer is required to extract data independently and blinded to ensure bias is minimised. (7) A list of excluded articles is available with reasons for exclusion. (8) The included studies are described in adequate detail as required to answer the review questions. (9) A satisfactory technique is used to assess the risk of bias (RoB) in individual studies that were included in the review. (10) The sources of funding for the individual studies included in the review are reported. (11) The RoB in individual studies is considered when interpreting or discussing the results of the review. (12) A satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review is provided. (13) If a quantitative synthesis was performed, an adequate investigation of publication bias (small study bias) is conducted and its likely impact on the results of the review is discussed. (14) Any potential sources of conflict of interest, including any funding received for conducting the review are disclosed.

### **3.2.7 Review Types**

There are a number of different review types. The depth and breadth of investigation distinguish these review types from each other as illustrated in Figure 3.2. In this section *breadth* indicates the extent of the field of inquiry and *depth* is used to indicate the detail of inquiry which, in combination, constitute the scope of the review. For example, a review with the aim to provide a compendium of all psychometric assessments currently in use would be considered broad. In terms of depth, the detail of describing these assessment measures would be the determining factor. Technical aspects, such as

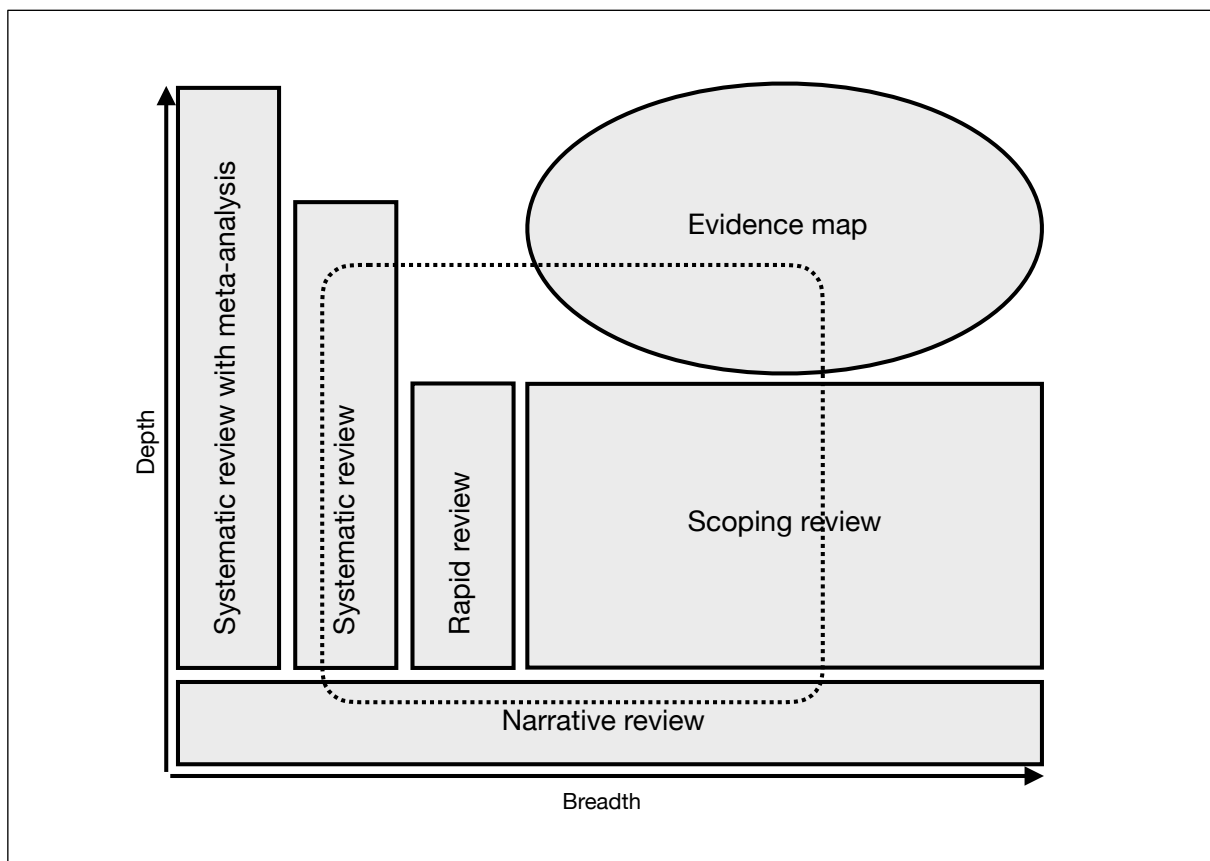


reliability, validity, normative data and standardisation methods would be considered more in-depth than a basic overview of the purpose of the measures.

*Heterogeneity* refers to a high degree of diversity or difference in the content, specifically. For example, a sample of research articles could have high heterogeneity in terms of age: the age group of half of the studies is between 18 years and 25; and the age group of the other half is between 55 and 65. In this sense heterogeneity is a characteristic of the data.

**Figure 3.2**

*Illustration of the Depth and Breadth of the Various Review Types*



As illustrated in Figure 3.2, the most in-depth and narrowly defined review type is a meta-analytical systematic review. Intuitively, the narrow area of investigation increases the likelihood of low data heterogeneity which, in turn, ensures a meta-analysis is possible. The broadest review type, with the primary aim of a general oversight, is the narrative review. The rapid review, scoping review, and systematic review with narrative synthesis can be heuristically categorised between these two extremes (Boland et al., 2017). An evidence map is a relatively new methodology that may form part of the systematic review and can

be described as the presentation of gaps in the research identified after synthesis (Miake-lye et al., 2016).

Individual reviews, although categorised as a specific review type by virtue of fulfilling specific criteria, may also contain elements from other review types. This is represented in Figure 3.2 by the dotted rectangle. Table 3.1 provides a comparative breakdown of the main elements and criteria of each review type.

**Table 3.1**

*Main Elements and Criteria of Various Review Types*

	<b>Systematic review (narrative synthesis or meta-analysis)</b>	<b>Scoping review</b>	<b>Rapid review</b>	<b>Narrative review</b>
<b>Clearly defined question</b>	Essential  Focused	Essential  Broad	Essential  Focused	Optional  Broad or focused
<b>Protocol</b>	Essential	Optional	Optional	Not required
<b>Explicit methodology</b>	Essential	Optional	Essential	Not required
<b>Search strategy</b>	Sensitive and specific	Broad with citation chaining	Limited	Researcher discretion used
<b>Inclusion and exclusion criteria</b>	Essential and pre-defined	Essential and may be post hoc if justified	Essential and narrow	Optional
<b>Screening and selection</b>	Explicit  Cross-checked	Explicit  Cross-checked	Explicit  Single researcher	Flexible  Single researcher
<b>Quality assessment</b>	Essential	Not required	Not required	Optional
<b>Data extraction</b>	Essential	May be iterative	Limited	Essential
<b>Analysis and synthesis</b>	Meta-analysis, or narrative, or qualitative	Descriptive, or analytical framework or thematic for the purpose of overview	Narrative only	Based on expert experience
<b>Timeframe</b>	Time-consuming	Variable	Variable	Variable
<b>Replication</b>	Replicable	Possibly replicable	Possibly replicable	Not easily replicable
<i>Note.</i> Adapted from <i>Doing a Systematic Review</i> , by Boland et al., 2017, p. 42-43.				

### **3.3 Methods**

#### **3.3.1 Introduction**

In this section I describe the procedures followed in the current study. A general overview of the entire process is presented, which is followed by detailed explanations of each step in the process.

#### **3.3.2 Overview of Procedures**

The review conducted for the present study conforms to all the requirements of a systematic review as presented in Table 3.1. A predefined protocol (see Appendix A) was compiled with clearly defined research questions to address the main objectives of the systematic review. These are to identify the available empirical studies related to substance dependence and the neuropsychological assessment of executive functions and, by the use of appropriate methods, to analyse and synthesise the evidence in order to delineate the current body of knowledge and address the current state of fragmentation. Furthermore, an explicit methodology was followed which included a search strategy that was both sensitive and specific. Inclusion and exclusion criteria for the screening and selection of the search results were predefined and explicit. All stages of screening and selection, data extraction and quality assessment were done by two reviewers. The extracted data were highly heterogenous as anticipated and, therefore, a narrative synthesis was conducted.

To ensure that the systematic review not only met the basic requirements of the methodology but also complied with quality criteria, the AMSTAR guidelines (Shea et al., 2017) described earlier in this chapter were used throughout the course of conducting the research.

The entire review process was conducted electronically. The software programme Mendeley (Elsevier, 2019) was used for reference management as it contains all the necessary features. These features include customisable organisation of options; automatic cloud storing and backup; use and synchronisation of data on numerous devices; and compatibility with other research information systems (RIS), such as Covidence (2019). The various software programs used for systematic reviews were considered (Columbia University Medical Center, 2018; Harvard Library, 2018; HLWIKI Canada contributors, 2018). Thereafter, Covidence was chosen based on the following important features:

- Cochrane recommends using Covidence for all new reviews to streamline the most labour intensive stages of a systematic review (The Cochrane Collaboration, 2018).
- Search results and documents can be easily imported.
- User-friendly interface with high customisability to suit the requirements of the specific review being conducted.
- The systematic review processes are streamlined
- Comprehensive training and tutorial videos are freely available online.
- More than one reviewer can work remotely on the systematic review.
- All voting is blinded to ensure decisions are not biased.
- All activities are recorded to ensure transparency.
- The entire review process is tracked, recorded and stored.

Data extraction and quality assessment was conducted using Google Forms. Although Covidence streamlined the screening and selection processes, the data extraction module of the software is primarily designed for intervention studies and only customisable to a limited degree. After a number of studies were piloted for data extraction on both Covidence and Google Forms, I decided that Google Forms would be more feasible for extracting data.

### ***3.3.3 Literature Search***

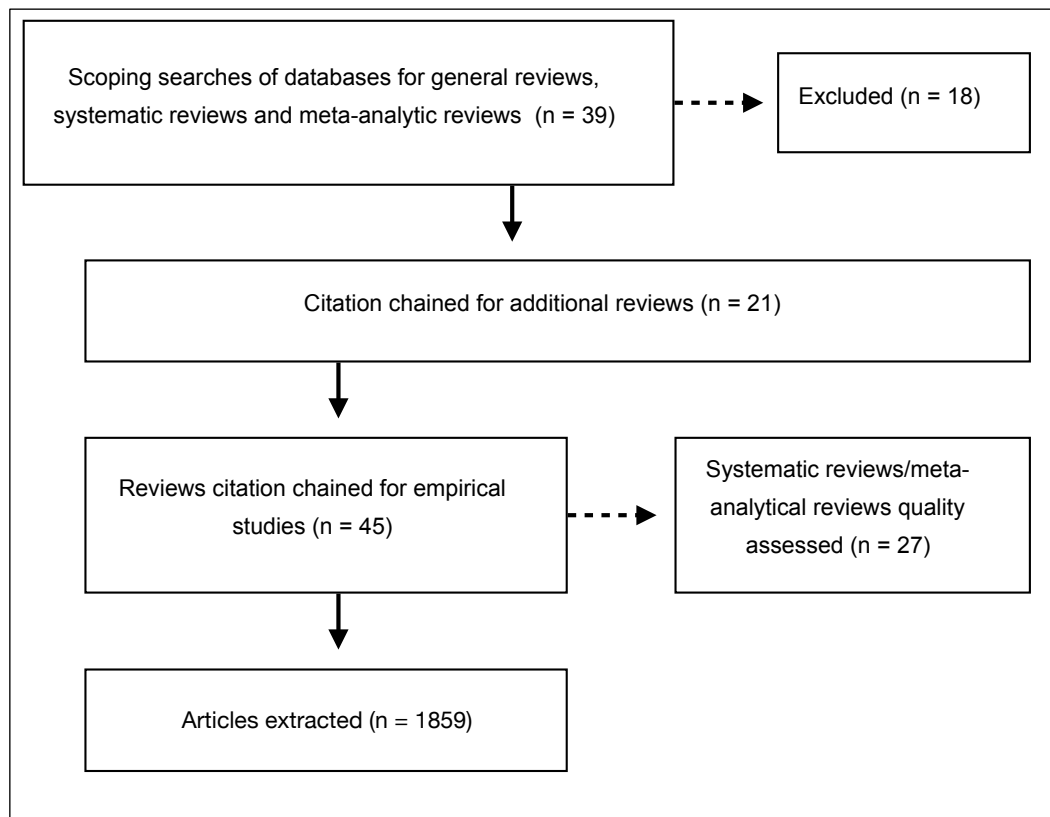
Two search methods were used in this systematic review. Citation chaining was conducted using existing systematic reviews and Boolean searches were carried out on both general and specialist electronic databases.

#### **3.3.3.1 Citation Chaining.**

Cribbin (2011) describes citation chaining as a method where citations within a seed article is searched to find articles that meet specific criteria. Snowballing can then be conducted, which entails performing the same citation chaining on the articles found from the seed article. Although citation chaining is not an explicit requirement for a systematic review it was conducted to ensure a higher likelihood that the relevant empirical studies would be included. The citation chaining process is presented in Figure 3.3.

**Figure 3.3**

*Flow Diagram of Citation Chaining Process*



Scoping searches were conducted on several databases for general reviews, systematic reviews and meta-analytic reviews using search terms related to the scope of the current systematic review (i.e., neuropsychological assessment, executive functions and substance dependence). Thirty-nine reviews were located. Of these reviews, 18 were excluded for not falling within the research scope. The 21 included reviews were citation chained as seed articles for additional reviews. Subsequently, snowball citation chaining was performed on the additional reviews. Twenty-seven reviews classified as systematic reviews or meta-analytic reviews were quality assessed using the AMSTAR criteria (Shea et al., 2017). Finally, 45 reviews were citation chained for empirical studies falling within the scope of this systematic review and a total of 1859 references were extracted.

### **3.3.3.2 Electronic Database Searches.**

Three electronic databases, PubMed, PsycINFO and MEDLINE were used to search for published literature. These databases were selected as they were most likely to contain the relevant studies for the scope of the systematic review. A list of search terms was compiled after consultation with an information scientist, conducting scoping

searches, referring to related existing reviews and consulting relevant glossaries. Three comprehensive international glossaries were consulted for terms linked to substance dependence (Australian Drug Information Network, 2016; National Institute on Drug Abuse, 2016; The National Center on Addiction and Substance Abuse, 2017). The substances have several commercial and street names and these may vary from country to country. It is improbable that a study title and abstract will contain only the street name or commercial name of a substance. Therefore, only the most commonly recognised of these names were included in the search term list. All the internationally recognised terms for the substances were included in the list. These search terms were combined with terms related to executive functioning when conducting searches, considering both specificity and sensitivity of results. The search terms are listed in Table 3.2.

**Table 3.2**

*Search Terms Used in MEDLINE, PubMed and PsycINFO*

<b>Substance dependence</b>			<b>Executive functioning</b>
addiction	alcohol	lsd	executive function
drug dependence	amphetamine	marijuana	cognition
drug abuse	ayahuasca	mdma	neuropsychology
substance dependence	barbiturate	mephedrone	neurocognition
substance abuse use disorder	benzodiazepine	mescaline	attention
	caffeine	methadone	decision making
	cannabinoid	methamphetamine	working memory
	cannabis	morphine	
	cathinone	nitrous oxide	
	cocaine	nyaope	
	codeine	opiate	
	crack	opioid	
	dmt	oxycodone	
	ecstasy	phencyclidine	
	flunitrazepam	psilocybin	
	ghb	rohypnol	
	heroin	salvia	
	ketamine	steroid	
	khat	tetrahydrocannabinol	
	kratom	tobacco	

A total of 494 searches were conducted during April and May 2019 using a Boolean strategy. All individual searches were timestamped and documented in detail. The results of each search were downloaded from the electronic database and saved in both a local drive and a cloud server for backup. The complete records of electronic database searches are publicly available at DOI: [10.13140/RG.2.2.35629.84964](https://doi.org/10.13140/RG.2.2.35629.84964)

### ***3.3.4 Screening and Selection***

As an overview, studies were included where the populations are humans presenting with substance dependence or substance use disorder and neuropsychological assessment of executive functions was administered. Studies with only animal models, neurocomputational models and other addictions were excluded (for example, gambling or internet gaming). Studies where instruments other than neuropsychological instruments were used exclusively, such as neuroimaging, biochemical or genetic methods, were also excluded. Studies were included with or without comparators (for example, the comparison between a treatment group and a control group; or the comparison between a treatment condition and a control condition). The measured outcomes of studies can be very different and therefore studies with any reported outcomes were included. These were, for example, related to adherence and relapse or the results of the neuropsychological assessment. With regard to study designs, publications with any study design were included with the one exception of qualitative designs. Studies that were conducted in any setting were included. These may be, for example, rehabilitation facilities, rural clinics, outpatient clinics, private practices and hospitals.

Ethical violations were considered an exclusion criterion. This includes any form of harm, coercion, deception, breach of privacy and confidentiality, fabrications, omissions and contrivances (Wagner et al., 2012). However, none of the studies screened required exclusion on ethical grounds. Studies with null or negative findings are less likely to be submitted or selected for publication in peer-reviewed journals (Boland et al., 2017). To somewhat counteract this publication bias, studies from both peer-reviewed and non-peer-reviewed journals were included. Finally, studies from any publication year and any language were included.

The screening and selection process of the systematic review is presented in Figure 3.4 using the PRISMA flow diagramme (Moher et al., 2009) and all the processes are described in detail in the sections that follow. In brief, a total of 16 265 references were

imported for screening from electronic database searches and reference chaining (described in more detail below).

**Table 3.3**

*Inclusion and Exclusion Criteria*

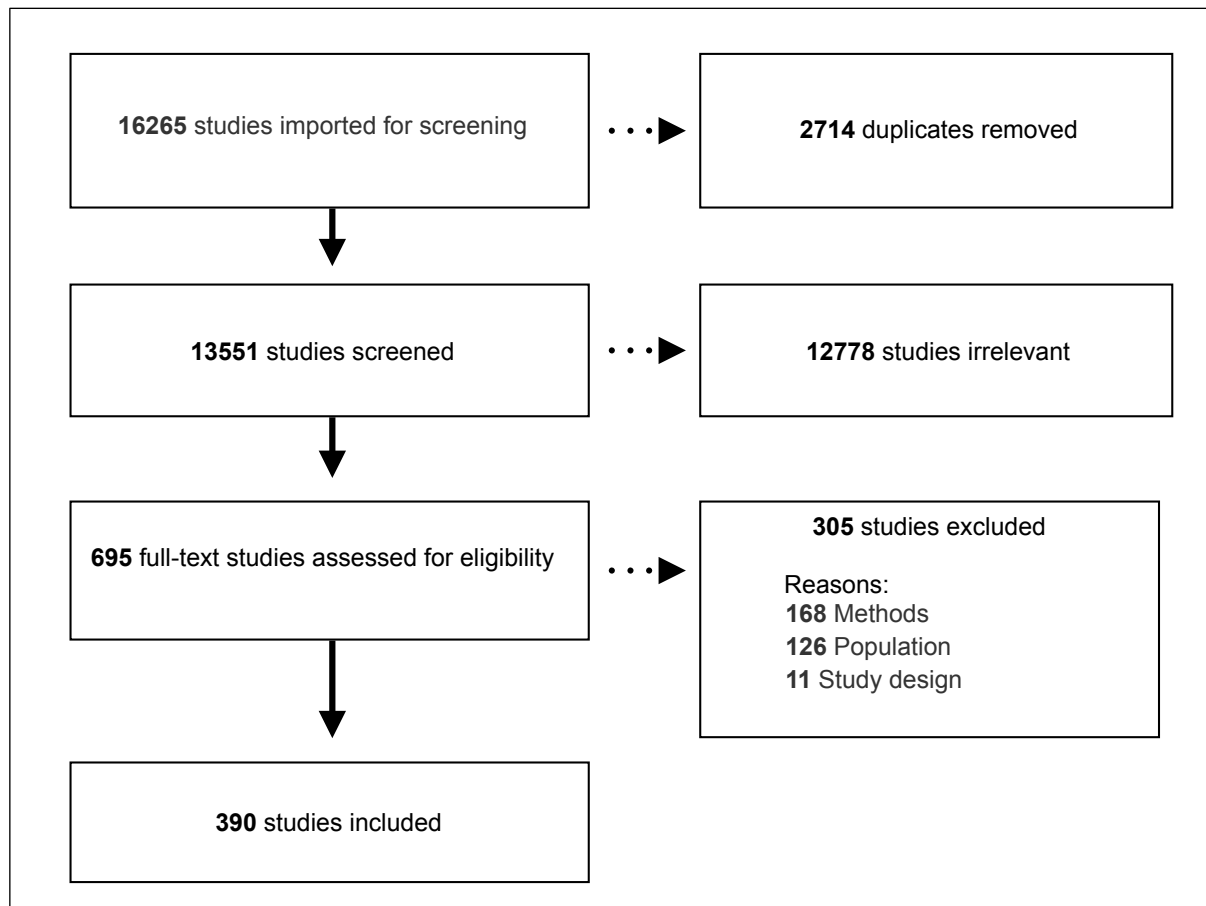
<b>Review Scope</b>		
<b>Executive functioning assessment of substance dependence individuals</b>		
	<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
<b>Population</b>	Human population;  Diagnosed with substance dependence; or diagnosed with substance use disorder	Animal models excluding human population;  Neurocomputational models excluding human population;  Other addictions (gambling, internet, gaming, etc.)
<b>Intervention (Assessment Measures)</b>	Neuropsychological assessment measures of (a) executive functioning; or (b) general cognition with executive function as a subcomponent. Or (c) attention; or (d) working memory; or (e) decision making as subcomponents of executive functioning	Neuroimaging, biochemical or genetic methods excluding neurocognitive assessment measures.
<b>Comparator</b>	All	None
<b>Outcomes</b>	All	None
<b>Study designs</b>	Randomised control trials Non-randomised control trials Cohort studies Case control studies Case series studies Cross-sectional studies Non-comparative studies Other (e.g. multi-method)	Studies that are exclusively qualitative
<b>Setting</b>	All	None
<b>Language</b>	All	None
<b>Period</b>	All	None
<b>Ethics</b>	Ethical conduct	Ethical violations*
* Harm, coercion, deception, breach of privacy and confidentiality, fabrications, omissions and contrivances.		



After 2 714 duplicates were removed, 13 551 titles and abstract were screened using the predefined inclusion and exclusion criteria as tabulated in Table 3.3. Following the exclusion of 12 778 studies, 695 full-text articles were assessed for eligibility. After the final exclusion of 305 full-text articles, data were extracted from 390 studies.

**Figure 3.4**

*PRISMA Flow Diagramme of the Identification of Studies*



The electronic files containing the records of titles and abstracts ( $n = 16\,265$ ) from both the citation chaining and electronic database searches were uploaded to the systematic review software, Covidence. After duplicates were removed ( $n = 2714$ ) the title and abstracts were screened for inclusion by two reviewers. This was done independently and blinded; in other words, information regarding the decisions of each reviewer was unavailable to the other reviewer. This ensures that bias is minimised by lowering the probability of following the decisions of the other reviewer as a shortcut. The second reviewer was selected from a number of undergraduate psychology students who

volunteered their services and, besides having a special interest in neuropsychology, was also highly motivated and dedicated from the onset.

All records were screened by me as first reviewer (n = 13 551) and a sample of records (n = 1117) was screened by the second reviewer. There was agreement between reviewers in 97.7 per cent of the records. Agreement was measured using Cohen's kappa with a score of 0.89. The minimum required kappa score for sample screening is 0.8 (Shea et al., 2017). It was therefore concluded that screening criteria were sufficiently clearly specified to allow for adequate agreement between the two reviewers. The conflicts were resolved and the records that did not meet inclusion criteria were excluded (n = 12 778).

The full-text articles for the included records were obtained electronically (where available – see below) and screened by two reviewers. Screening was done independently and blinded. All articles were screened by me (n = 695) and a sample of records (n = 271) was screened by the second reviewer. There was agreement between reviewers in 93.5 per cent of the articles. Agreement was measured using Cohen's k. The agreement score was 0.85 with the minimum required kappa score for sample screening being 0.8. The conflicts were resolved and the articles that did not meet inclusion criteria were excluded (n = 305).

Full-text papers were electronically obtained through the university library. The library staff were contacted to assist with obtaining papers through the inter-library loan system in cases where the full-text papers were not available through the databases. A total of 97 articles were not available and these papers were also requested directly from the authors via email or online academic networking portals such as *Researchgate*. The same procedure was followed for papers that were published in languages other than English. Of the 773 included titles and abstracts, 68 full-text papers could not be located and 10 papers were published in foreign languages with no English versions available.

The bibliography of the 390 included empirical studies is publicly available at DOI: [10.13140/RG.2.2.17030.73285/1](https://doi.org/10.13140/RG.2.2.17030.73285/1)

The list of full-text articles that were not available for screening is publicly available at DOI: [10.13140/RG.2.2.14658.32962](https://doi.org/10.13140/RG.2.2.14658.32962)

### **3.3.5 Data Extraction**

Pilot data extraction was performed on a number of studies using both the Covidence data extraction module and a custom designed data extraction form on Google

Forms (Table 3.4). Using Google Forms proved to streamline the process better than Covidence. Therefore, data extraction and quality assessment were subsequently conducted on Google Forms by both reviewers. Data extraction was done electronically by copying the relevant data from each electronic article and pasting it in the online data extraction form. This minimised the potential copying errors of paper data extraction. The extracted data were stored in a database located on both a local drive and a cloud server for backup. Because of the large number of studies included ( $n = 390$ ), it was not feasible to conduct data extraction in duplicate when considering time constraints. Therefore, I conducted the majority of data extraction ( $n = 310$ ) and randomly allocated a sample of articles ( $n = 80$ ) to the second reviewer. The complete data tables are publicly available at the following URL: [https://www.researchgate.net/publication/338479397\\_Data\\_Tables](https://www.researchgate.net/publication/338479397_Data_Tables)

**Table 3.4**

*Data Extraction Form*

<b>Heading</b>	<b>Description of required data</b>
Title	<i>Title of the publication</i>
Authors	<i>Authors of the publication</i>
Country	<i>Country where the research was conducted</i>
Setting	<i>Settings of participants during study (community, clinic, etc.)</i>
Study aims	<i>The reported aims of the research</i>
Study design	<i>The study design of the research</i>
Theory of executive functions	<i>The theory of executive functions used to support the research</i>
Funding and conflict of interest	<i>Declaration of conflict of interest and list of funding sources</i>
Basic demographics of participants	<i>Minimum of age, gender and education level</i>
Comorbidities	<i>Any other medical conditions of participants</i>
Substance(s)	<i>List of substances investigated in study</i>
SUD/dependence related diagnoses	<i>Instruments used to diagnose substance abuse or dependence</i>
Inclusion criteria	<i>Criteria used to include research participants</i>
Exclusion criteria	<i>Criteria used to exclude research participants</i>
Group differences	<i>How groups were defined in the study</i>

Attrition	<i>Any participants that were excluded or withdrew</i>
Interventions	<i>Any experimental conditions assigned to the participants</i>
Neuropsychological assessment instruments of executive functioning	<i>List of neuropsychological instruments reported to assess executive functioning</i>
Findings - Neuropsychological assessment instruments of executive functioning	<i>The findings of neuropsychological instruments reported to assess executive functioning</i>
Other neuropsychological assessment instruments	<i>List of instruments reported to assess other neuropsychological domains</i>
Findings – Other neuropsychological assessment instruments	<i>The findings of instruments reported to assess other neuropsychological domains</i>
Study limitations	<i>Reported limitations of the study</i>

### 3.3.6 *Quality Assessment*

I conducted a pilot for data extraction and found it to be more feasible to perform quality assessment in conjunction with the data extraction and not as a completely separate process altogether. The main reason for this is because the reviewer is most familiar with each individual study directly after data extraction and therefore better able to make appropriate judgements, as opposed to a separate process of screening each article and then making judgements.

The quality assessment entailed making judgements about the likelihood of potential risk of bias within each study. Because all study designs except qualitative designs were included in the systematic review, a customised assessment tool was designed. Various risk of bias tools were consulted to compile the assessment criteria (Critical Appraisal Skills Programme, 2018; Thomas et al., 2004; Zaza et al., 2000). The following items were included to assess the risk of bias of the included studies: (1) *Selection bias* was determined by evaluating if the participants in the study are representative of the target population and if appropriate recruitment methods were used to ensure this; (2) *Attrition bias* was determined by evaluating the drop-out or withdrawal rate of participants and if this was considered when data were analysed; (3) *Data collection bias* was determined by evaluating if the data collection instruments and methods were shown to be valid and reliable; (4) *Reporting bias* was determined by evaluating if all the outcomes stated to be measured were reported, even outcomes with null or negative findings; (5) *Confounders* was determined by evaluating if the participant characteristics

were matched or any other variables that may have a confounding effect; (6) *Contamination or co-intervention* was determined by evaluating if the participants received any unintended interventions or treatments; (7) *Bias in analysis* was determined by evaluating if the appropriate methods were used to analyse the data and all the data were reported; and (8) *Funding bias* was determined by evaluating if the any possible conflict of interests exist based on reported funding or affiliations.

### **3.3.7 Data Analysis and Synthesis**

The raw data captured on the online data extraction form (Table. 3.4) were automatically stored on a secure online database. Upon completion of all data extraction, the raw data were downloaded in a tabulated format. Data analyses was done systematically in accordance with the research questions of the review. The data were somewhat inconsistent because, in addition to the large number of included articles, the articles originated from 121 different journals, 39 different countries and a publication date range of 34 years.

The variation within the investigated categories had to be calculated through data analyses to reveal possible gaps and the extent of these gaps. Therefore, the index of qualitative variation (IQV) was used, where feasible, to calculated variability for nominal variables (Frankfort-Nachmias & Leon-Guerrero, 2009). This index ranges from no variation (0.00), where all the cases in the distribution are in one category, to maximum variation (1.00), where all the cases are distributed equally in all the possible categories (1.00). It is important to note that where the frequencies were calculated and data from a single study could be categorised into more than one category, the IQV would not be a valid measure of variability and was therefore not used. This is because the IQV reflects the variability of the differences between categories relative to the maximum possible differences in each distribution (Frankfort-Nachmias & Leon-Guerrero, 2009).

#### **3.3.7.1 Age.**

In the extracted data, entries for sample ages were variable; for example, the average age of each sample group or the combined average age of all sample groups. However, the entries with a combined average age of all sample groups excluded the healthy control groups. Therefore, this was the most detailed data that could be consistently validated across all entries and the data were coded to the average age of the combined sample groups (excluding healthy controls). The data could be further

categorised into age groups with intervals of five years, and the number and percentage of studies per age group was calculated. The IQV was used as a measure of variability.

#### **3.3.7.2 Education.**

Education data in some entries were explicit years, and in other entries *more than* or *less than* a number of completed educational years. The most detailed data that could be validated consistently across the dataset for education were categories of less than nine years (<9), between nine years and twelve years (9-12), and more than twelve years (>12). The data for education were coded to these categories, and the number and percentage of studies per educational-level category was calculated. The IQV was used as a measure of variability.

#### **3.3.7.3 Gender.**

The dataset for gender also contained high variability; for example, as a percentage or a ratio for specific sample groups or the combined sample groups (omitting number of participants per sample group in some studies). Therefore, the most detailed data that could be validated consistently across all data were categories of majority males (>50% males), majority females (>50% females), only females (100% females), only males (100% males), and equal females and males (50% females, 50% males). The number and percentage of studies per category was calculated. The IQV was used as a measure of variability.

#### **3.3.7.4 Substances.**

The data of substances were coded and each entry was categorised according to the investigated substance use disorder or substance dependence type. The IQV was used as a measure of variability. However, one third of the data entries investigated multiple substances and, therefore, it was necessary to determine the combined frequency of each substance category in all the data. Data coding was refined by listing all the investigated substances in all the data and determining the frequency of each substance. The number and percentage of each substance category was calculated.

#### **3.3.7.5 Comorbidities.**

All the possible comorbidities from the extracted data were coded and the following categories were compiled based on this list of comorbidities: psychosis/schizophrenia, human immunodeficiency virus (HIV), Korsakoff syndrome, attention deficit hyperactivity disorder (ADHD), mood disorders, personality disorders,

various psychiatric (multiple and variable diagnoses), Alzheimer's disease/dementia, and other (single studies with conditions such as childhood trauma, homelessness, learning disabilities, liver cirrhosis, intellectual disability, mild traumatic brain injuries, neurocognitive disorders, obsessive-compulsive disorder, and viral infection). The number and percentage of studies per category was calculated.

### 3.3.7.6 Substance Use and Dependence Criteria.

The measurements to establish substance dependence in the data were coded. Because more than one measurement was used in some studies, the combined frequency of each measurement was calculated in all the data.

### 3.3.7.7 Neuropsychological Assessment Instruments.

The number and type of neuropsychological instruments varied significantly. Therefore, every assessment instrument in the data tables was coded and the combined frequency of each instrument in all the data was calculated. Individual instruments (or modules) were selected for administration from various assessment batteries in respective studies. However, it was necessary to determine the use of instruments most frequently used for the assessment of executive functions and therefore the frequencies of these individual instruments or modules were also calculated. These are tabulated in Table 3.5.

**Table 3.5**

*Executive Function Assessment Instruments of Modules within Select Neuropsychological Assessment Batteries*

<b>Neuropsychological Assessment Battery</b>	<b>Executive function assessment instruments/modules</b>
Brief Assessment of Cognition in Schizophrenia (BACS)	<ul style="list-style-type: none"> <li>• Tower of London (TOLN)</li> <li>• Controlled Oral Word Association Test (COWAT)</li> </ul>
Behavioural Assessment of the Dysexecutive Syndrome (BADS)	<ul style="list-style-type: none"> <li>• Temporal Judgement (TJ)</li> <li>• Rule shift cards (RSC)</li> <li>• Action program (ACTP)</li> <li>• Key Search (KEY)</li> <li>• Zoo Map (ZOO)</li> <li>• Modified six elements (M6)</li> <li>• Dysexecutive questionnaire (DEX)</li> </ul>
Delis-Kaplan Executive Function System (D-KEFS)	<ul style="list-style-type: none"> <li>• Twenty questions test (DKEFS-20)</li> <li>• Color-Word Interference Test (DKEFS-CW)</li> <li>• Design Fluency (DKEFS-D)</li> <li>• Proverbs test (DKEFS-P)</li> </ul>

	<ul style="list-style-type: none"> <li>• Sorting test (DKEFS-S)</li> <li>• Tower Test (DKEFS-T)</li> <li>• Trail Making Test (DKEFS-TMT)</li> <li>• Verbal Fluency (DKEFS-VF)</li> </ul>
Cambridge Neuropsychological Test Automated Battery (CANTAB)	<ul style="list-style-type: none"> <li>• Cambridge Gambling Task (CGT)</li> <li>• Intra/Extra Dimensional Set Shift (IED)</li> <li>• Multitasking Test (MTT)</li> <li>• One-Touch Stockings of Cambridge (OTS)</li> <li>• Spatial working memory (SWM)</li> <li>• Stockings of Cambridge (SOC)</li> <li>• Stop Signal Task (SST)</li> </ul>

### **3.3.7.8 Theories of Executive Functioning.**

All the possible constructs used to describe or define executive functioning in the data tables were coded and the frequency of use of each construct was calculated.

### **3.3.7.9 Settings.**

The data for settings were coded and categorised into treatment facilities (not specified), inpatient, outpatient, day clinic, correctional facility, community (no treatment specified), and various categories with a combination of the latter. Thereafter, the total number and percentage of studies for each setting category was calculated. The IQV was used as a measure of variability.

### **3.3.7.10 Countries.**

The country that each study was conducted in was coded and the frequency was calculated. The countries were also categorised into the major global regions, namely Africa; Asia; Europe; Latin America and the Caribbean; North America; Oceania; and International and the percentage of studies per region was calculated. The IQV was used as a measure of variability.

### **3.3.7.11 Study Designs**

The primary study design used in each study was coded, and the frequency and percentage of each study design was calculated. The IQV was used as a measure of variability.

### **3.3.7.12 Comparators.**

Because of the high variability in comparator data, it was not possible to code each datum into a distinctive category. Instead, the frequency of use of the each coded comparator in all the data was calculated. The comparator categories were: (1) healthy



control group; (2) different substance group; (3) different use group; (4) different exposure history group; (5) control intervention/placebo group; and (6) different outcome group. The frequency was calculated of each of the latter categories.

#### **3.3.7.13 Risk of Bias.**

There were eight categories for risk of bias, namely selection bias; attrition bias; data collection bias; reporting bias; confounders; contamination or co-intervention; bias in analysis; and funding bias. For each category of each study the data entry options were *low*, *high* or *unclear/unknown*. The total number of each data entry for each category was calculated. Thereafter, the percentage of each data entry for each category was calculated.

#### **3.3.7.14 Findings.**

The high baseline and design-related heterogeneity of the included studies made it unfeasible to combine the statistical results through meta-analysis. Therefore, the study results were analysed by coding and categorising the results related to the relationship between executive functions and substance dependence in the extracted data of the respective studies. The results were considered either a reported causality or correlation between the variables. These were categorised as (1) a relationship between lower executive functioning scores and substance disorders; (2) a relationship between higher executive functioning scores and substance dependence; (3) no relationship between executive functioning scores and substance dependence; (4) mixed or inconclusive findings; and (5) other (individual studies with no explicit results for an executive functioning and substance dependence relationship). The total number and percentage of each findings category was calculated.

#### **3.3.7.15 Cross-tabulation.**

The study design categories and substance categories were cross-tabulated to determine the number and percentage of each study design per substance category; the substance categories and findings categories were cross tabulated to determine the number and percentage of each findings category per substance category; and, the findings categories were cross-tabulated with the study design categories to determine the number and percentage of each findings category per study design category.

### **3.3.8 Ethical Considerations**

Ethical approval for the systematic review was obtained from the UNISA Department of Psychology College of Human Science Ethics Committee (Appendix B).

The ethical considerations of each included study of the proposed review was considered during quality assessment and data analysis. These included any form of harm, coercion, deception, breach of privacy and confidentiality, fabrications, omissions and contrivances. To the best of that which could be ascertained only research studies conducted ethically were included in this review.

This study was partially funded by the Student Funding Directorate of the University of South Africa. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Chapter 4: Results

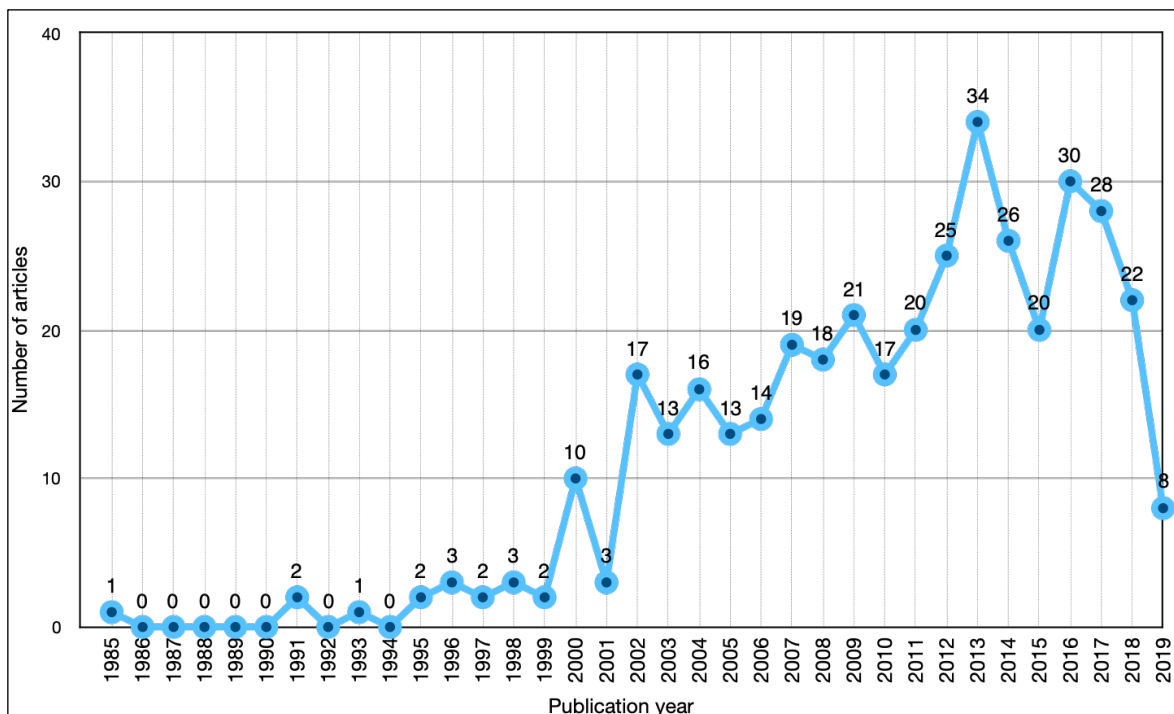
### 4.1 Introduction

As described in the previous chapter, 390 studies were identified that met all of the criteria for inclusion, namely the assessment of executive functioning in substance dependence populations using neuropsychological instruments. In this chapter, I present the findings that answer the research questions, as formulated in the protocol (see Appendix A). These findings include the demographics and other characteristics of the population samples within the research studies; the methods for diagnostic and neuropsychological assessment; the general study characteristics such as study designs, settings and countries; and finally, the results from the research studies pertaining to executive functioning and substance dependence.

### 4.2 Publication Characteristics of Included Articles

**Figure 4.1**

*Number of Published Articles per Year (1985-2019)*



To somewhat address publication bias, as proposed in the protocol, there was no restriction for including studies from non-peer-reviewed journals. Notwithstanding, after

analysis it was established that all the included articles were published in peer-reviewed journals. There was also no restriction for publication years. The date range for the included studies is 1985 to 2019 and Figure 4.1 illustrates the trend of studies published per year. The graph shows the number of published articles have increased over the years and especially between 2000 and 2019. It should be noted that the literature search was conducted in May 2019 and, therefore, the actual number of articles for 2019 is likely to be higher.

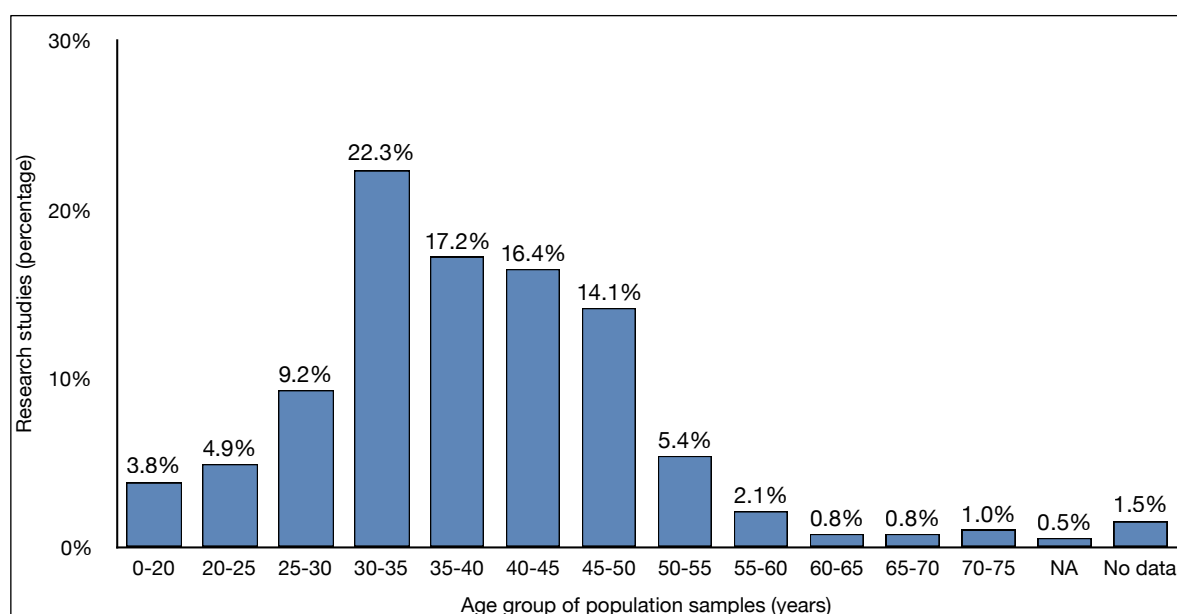
### 4.3 Demographics of Samples

Because of the high heterogeneity of the research studies, the reporting of sample ages also differs considerably in terms of the comparator groups and study designs. In each study, however, the groups were matched. Therefore, the data of all the groups in each study were combined and the mean value was used for age and education, whereas percentage was used for gender. In longitudinal studies, the values reported with first assessment was used. One study followed samples from birth and another from age five with multiple assessments throughout lifetime. For these two outliers, age and education were categorised as not applicable.

#### 4.3.1 Age

**Figure 4.2**

*Percentage of Research Studies per Age Group*

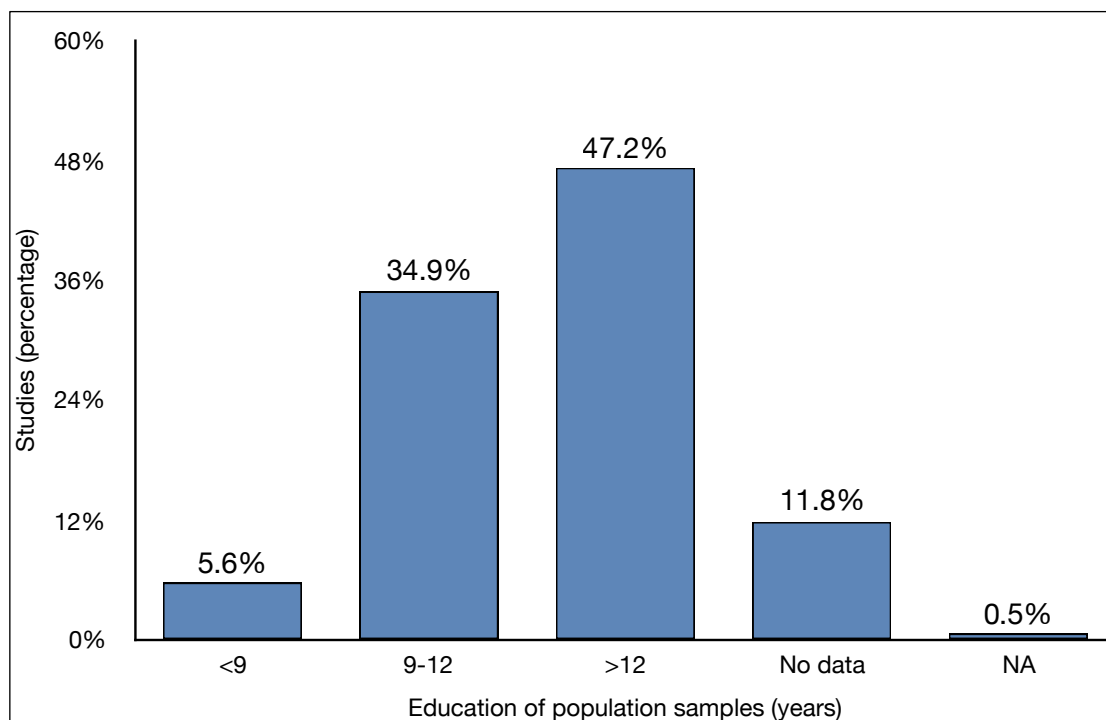


The mean age of the combined sample groups in each study was used to determine the percentage of studies per age group presented in Figure 4.2. Seventy per cent of all studies (n=273) had a mid-adulthood sample age, ranging between 30 and 50 years. Only 3.8 per cent of studies had a sample consisting of adolescents, younger than 20 years (n=15). Fourteen per cent had a sample of early-adulthood, 20 to 30 years (n=55) and 9.3 per cent for senior-adulthood, older than 50 years (n=39). The index of qualitative variation (IQV) (Frankfort-Nachmias & Leon-Guerrero, 2009) was used to establish the variability in the distribution of sample ages. An unequal distribution on the age-group categories was revealed by a variability of 0.92.

#### 4.3.2 Education

**Figure 4.3**

*Percentage of Research Studies per Education Level*



The mean education level of the combined sample groups in each study was used to determine the percentage of studies per education category (years of education) presented in Figure 4.3. Almost half of the studies (47.3%) had samples with an educational level of more than 12 years (n=184) and 34.9 per cent had samples that completed some level of secondary education (n=136). Forty-six studies (11.8%) did not report the level of education of population samples. The index of qualitative variation was

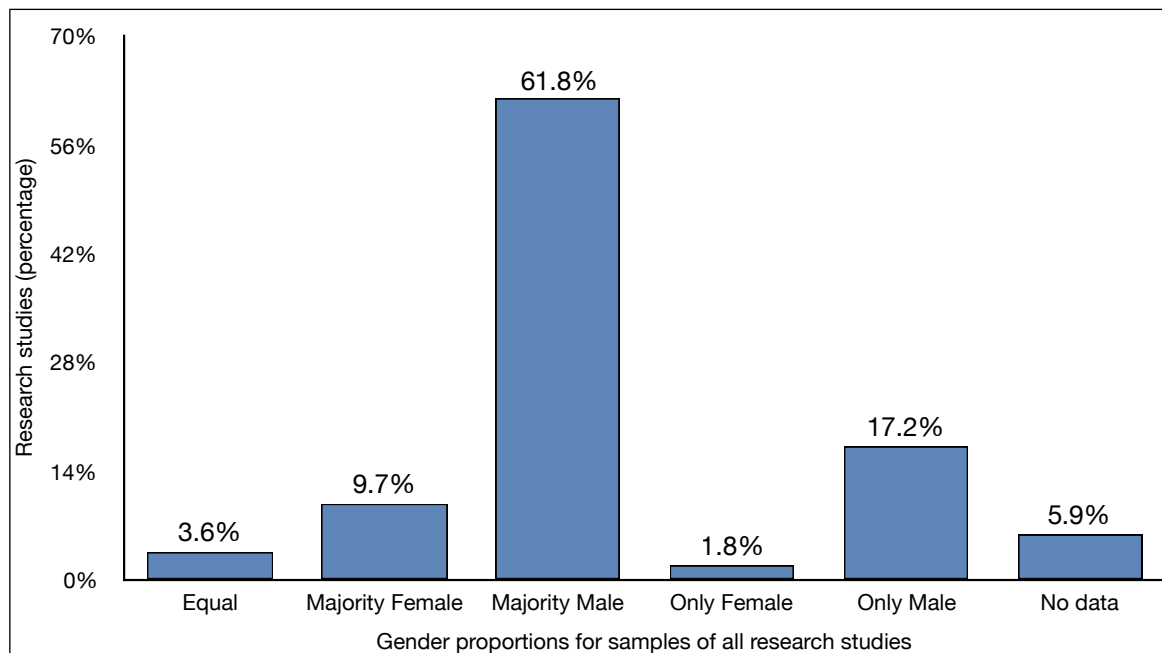
used to calculate the variability of 0.80 which revealed an uneven distribution on the categories for education.

#### 4.3.3 Gender

The gender proportion (percentage of individuals per gender) of the combined sample groups in each study was used to determine the percentage of studies per gender proportion category presented in Figure 4.4. Seventy-nine per cent of the studies had a combined sample consisting of more males than females ( $n=308$ ). Of these studies, 67 (17.2%) was categorised as having exclusively-male samples and 241 studies (61.8%) was categorised as having majority-male samples. Only 59 studies had samples containing females, with seven exclusively female. Twenty-three studies (5.9%) did not report on the genders of samples. A variability score of 0.69 revealed a significant unequal distribution on the gender proportion categories as determined by the index of qualitative variation.

**Figure 4.4**

*Percentage of Research Studies per Gender Proportion Category*



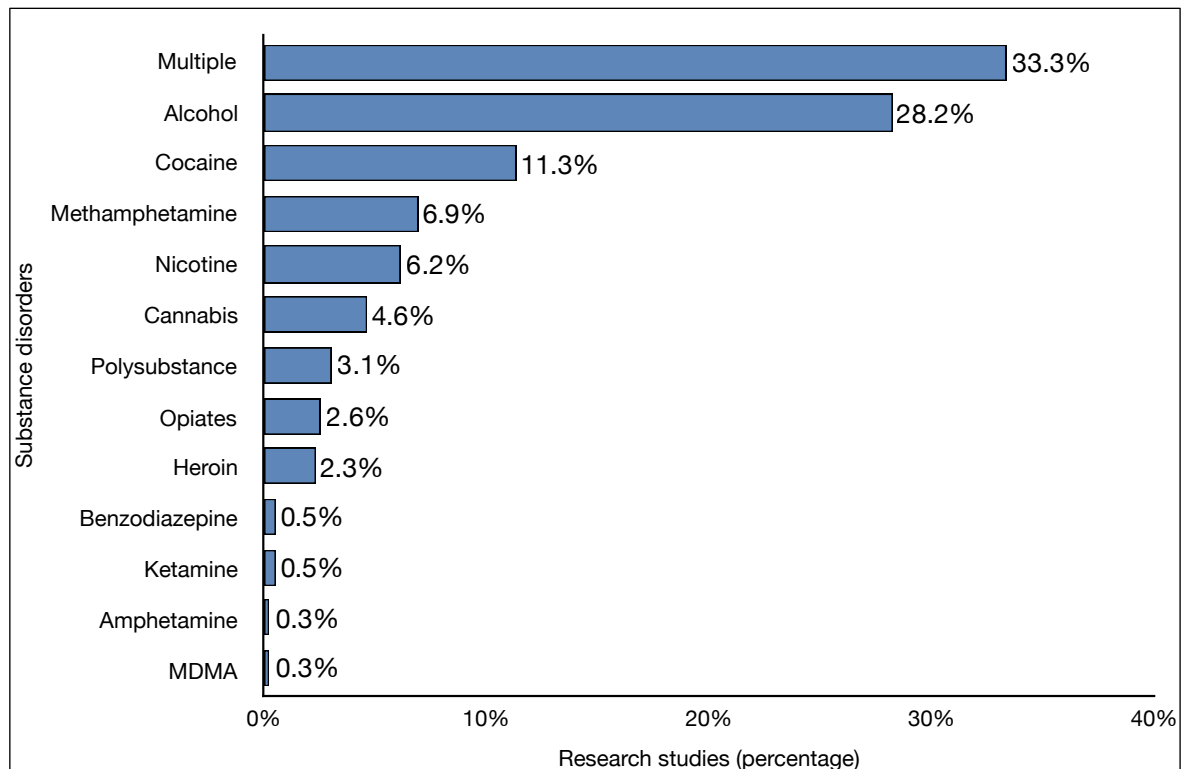
#### 4.3.4 Substances

The research studies were categorised according to the specific substance disorders of each study and Figure 4.5 illustrates the percentage of studies per category. One third of the studies ( $n=130$ ) investigated multiple substance-disorders followed by 28.2 per cent ( $n=110$ ) for alcohol disorders, exclusively. Only a small number of studies investigated

benzodiazepine (n=2), ketamine (n=2), amphetamine (n=1), and MDMA (n=1), exclusively. The variability of the distribution of 0.85 was calculated using the index of qualitative variation and revealed an unequal distribution on the substance disorder categories.

**Figure 4.5**

*Percentage of Studies per Substance Disorder*

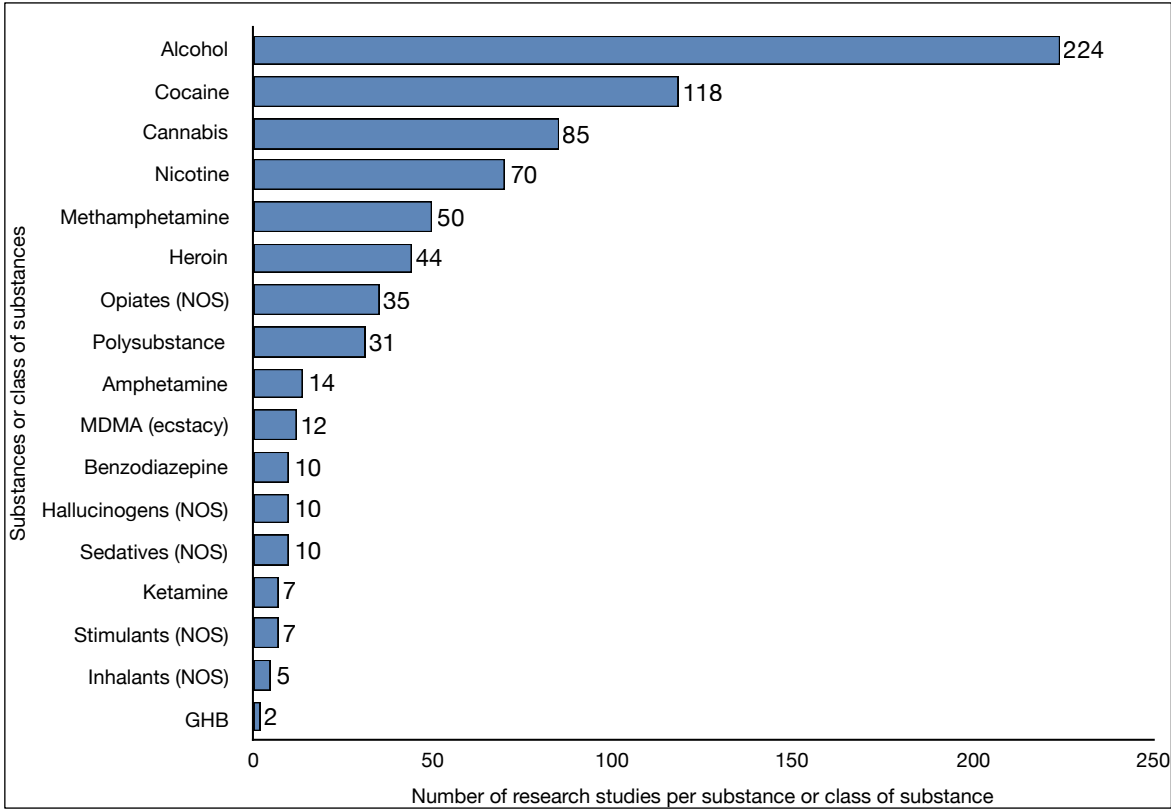


Because of the large number of studies investigating multiple substance-disorders and some with polysubstance disorders, it was necessary to also establish the frequency of investigation of each substance. Additionally, in cases where classes of substances were investigated and the individual substances not explicitly specified, the substance class was used. This provides the total number of studies per substance or category; or the total number of each substance dependent population. The findings from this analysis are presented in Figure 4.6.

When the frequency of each substance or class of substance was calculated it was revealed that alcohol remained the most investigated with 57.4 per cent of the studies or 224 population samples. There are studies with sub-samples of benzodiazepine (n=10), ketamine (n=7), amphetamine (n=14) and MDMA (n=12) which increases the small number of these studies investigating the substances exclusively. Similarly, the number of

studies investigating cannabis increased to 85 in contrast to only 18 for cannabis exclusively.

**Figure 4.6**  
*The Number of Population Samples for Each Substance or Class of Substances*



*Note.* NOS = Not otherwise specified. MDMA = 3,4-Methylenedioxymethamphetamine. GHB = gamma-hydroxybutyrate.

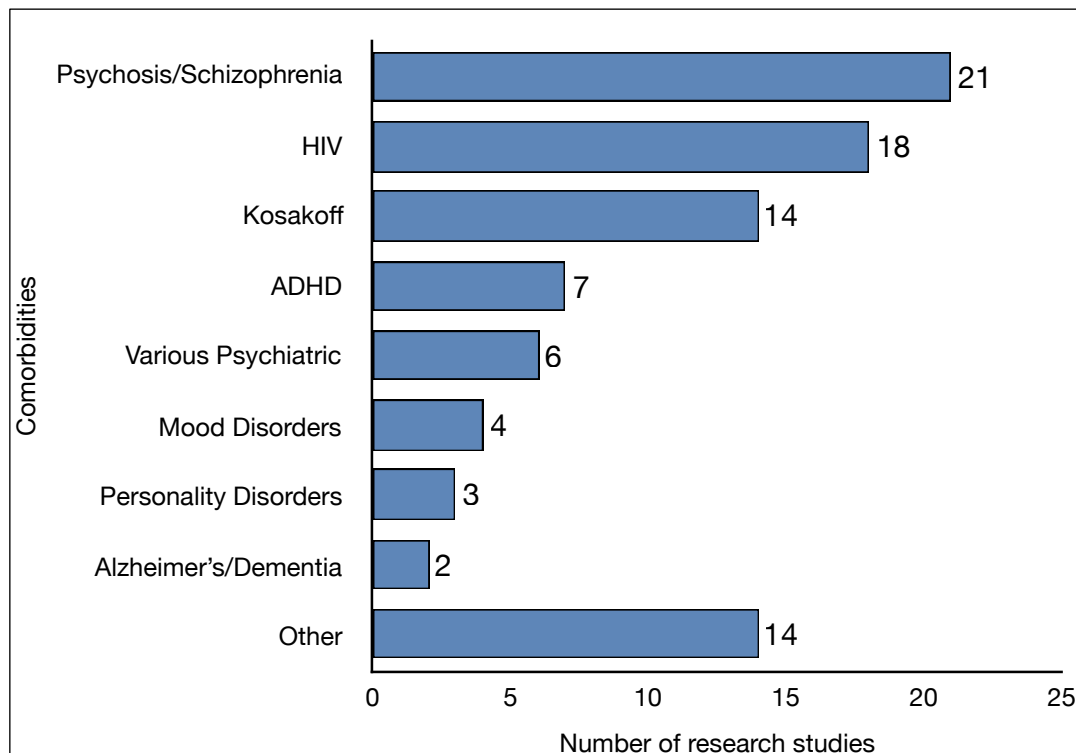
#### 4.3.5 Comorbidities

There were 89 research studies that investigated specific comorbidities in conjunction with the substance disorders. The number of studies for the various comorbidities is illustrated in Figure 4.7. These studies had either substance dependent sample groups with comorbid conditions or substance dependent comparison groups with these conditions. Psychosis/schizophrenia (n=21), human immunodeficiency virus (n=18) and Korsakoff syndrome (n=14) were the main conditions investigated. The Other category included single studies with comorbid childhood trauma, homelessness, learning disabilities, liver cirrhosis, intellectual disability, mild traumatic brain injuries, neurocognitive disorders, obsessive-compulsive disorder, and viral infection.



**Figure 4.7**

*Number of Studies Investigating Comorbidities*



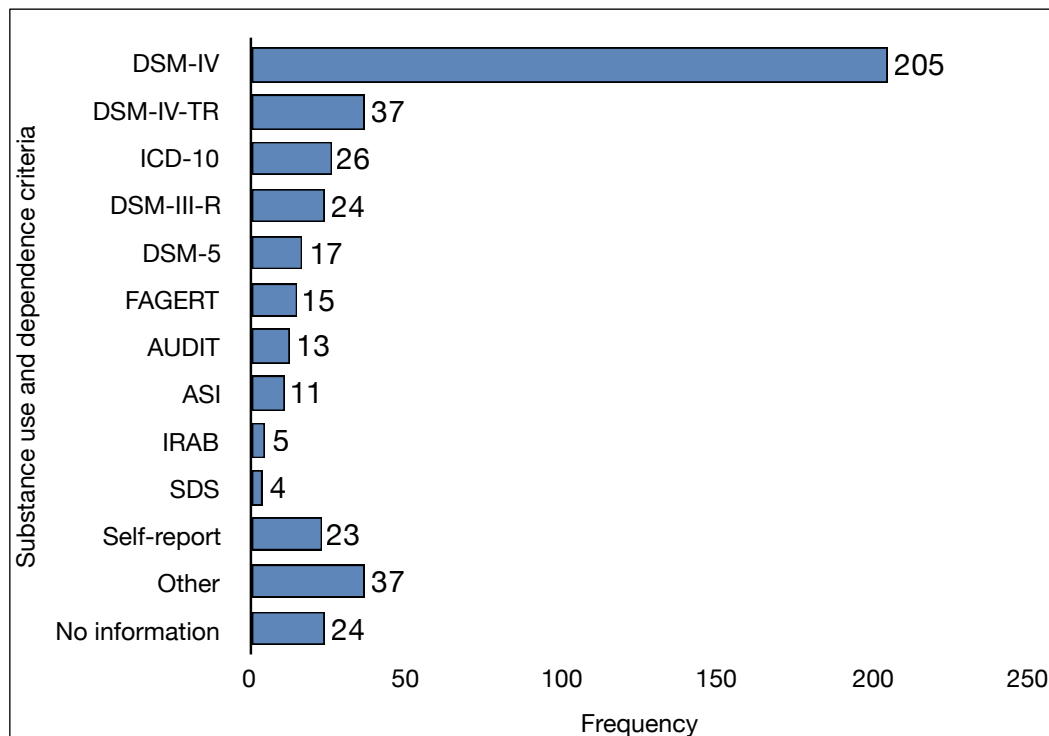
## **4.4 Assessment Instruments and Criteria Used in Studies**

### **4.4.1 Substance Use and Dependence Criteria**

Thirty-six different criteria were used to determine substance use and dependence in the research studies. These included formal assessment measures and self-report questionnaires. Because a proportion of studies used more than one measure the frequency of use had to be established. These frequencies are graphed in Figure 4.8 with measures used less than four times combined in the Other category. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria were used in 205 research studies, accounting for 52.6 per cent of all the studies. Seventy-three per cent of the studies (n=285) used the DSM criteria in general (editions III, III-R, IV, IV-TR, or V). In comparison, the criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) was used in only 26 studies (6.7%). Although many of the measures and criteria rely on self-reporting, twenty three studies used self-reporting as a method to determine substance use without specifying the structure of this measure. Twenty-four studies (6%) did not report on the substance-related criteria or assessment.

**Figure 4.8**

*Substance Use and Dependence Criteria Frequency of Use*



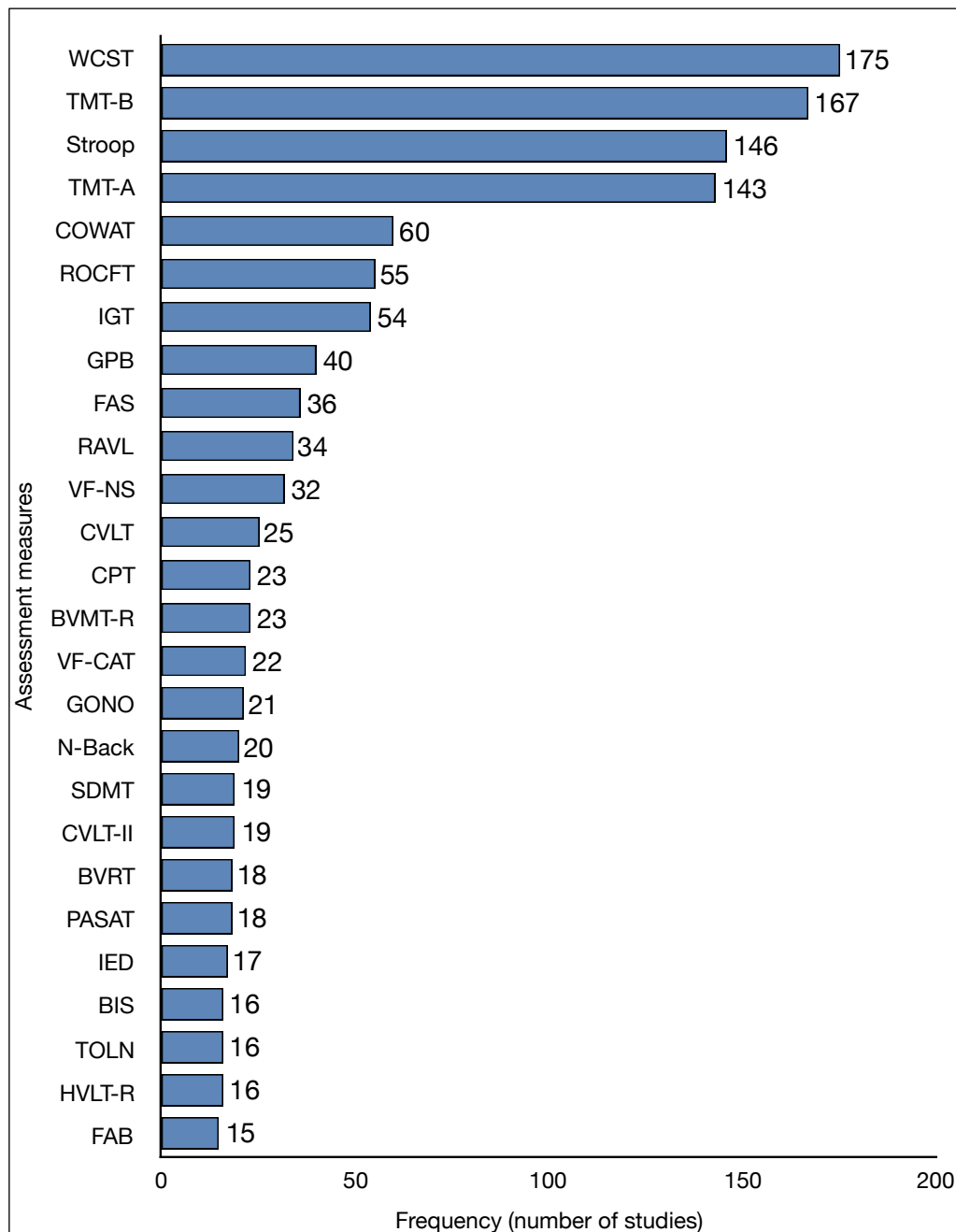
*Note.* DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition. DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision. ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision. DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, third edition, revised. DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, fifth edition. FAGERT = Fagerström test of nicotine dependence. AUDIT = Alcohol Use Disorders Identification Test. ASI = Addiction Severity Index. IRAB = Interview for Research on Addictive Behavior. SDS = Severity of Dependence Scale.

#### **4.4.2 Neuropsychological Assessment Instruments**

A total of 248 neuropsychological assessment instruments and batteries were used in the 390 research studies. Because the number and combination of assessment instruments varies from one study to the next it was necessary to determine the frequency of use for each instrument in all the studies. The assessment instruments used more than 14 times are graphed in Figure 4.9. The assessment batteries for general cognition are not included in the graph; however, the comprehensive table of all neuropsychological assessment instruments is publicly available at DOI: [10.13140/RG.2.2.11997.56800/1](https://doi.org/10.13140/RG.2.2.11997.56800/1). The assessments that were used most frequently were the Wisconsin Card Sorting Test (n=175, 45.9%), the Trail Making Test Part B (n=167, 42.8%), the Stroop Test (n=146, 37.4%) and the Trail Making Test Part A (n=143, 36.7%).

**Figure 4.9**

*Most Frequently Used Neuropsychological Assessment Instruments*



*Note.* WCST = Wisconsin Card Sorting Test-64. TMT-B = Trail Making Test part B. Stroop = Stroop Color-Word Test. TMT-A = Trail Making Test part A. COWAT = Controlled Oral Word Association Test. IGT = Iowa Gambling task. ROCFT = Rey–Osterrieth Complex Figure Test. GPB = Grooved Peg Board. FAS = FAS Verbal fluency. RAVL = Rey Auditory Verbal Learning Test. VF-NS = Verbal Fluency (not specified). CVLT = California Verbal Learning Test. CPT = Continuous performance task. BVMT-R = Brief Visuospatial Memory Test—Revised. VF-CAT = Verbal Fluency Category Test. GONO = Go/No Go task. N-Back = N-Back continuous performance task (including 2-back version). SDMT = Symbol Digits Modalities Test. CVLT-II = California Verbal Learning Test-II. PASAT = Paced Auditory Serial Addition Task. IED = Intra/Extra

Dimensional Set Shift (CANTAB) = BVRT = Benton Visual Retention Test. BIS = Barratt Impulsiveness Scale. TOLN = Tower of London. HVLT-R = Hopkins Verbal Learning Test—Revised. FAB = Frontal Assessment Battery.

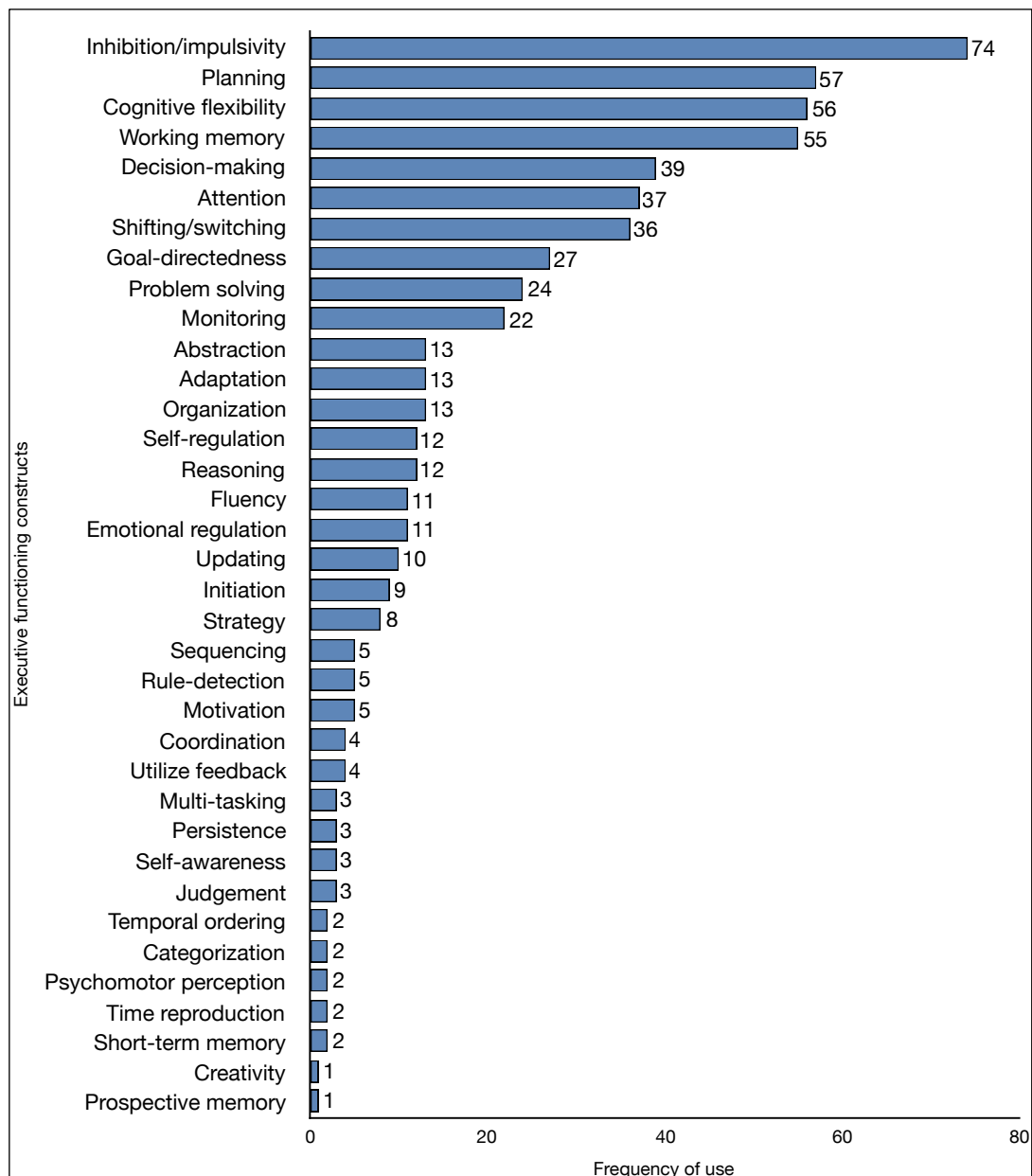
## 4.5 General Characteristics of Studies

### 4.5.1 Theories of Executive Functions

The extracted data were analysed to distinguish studies that used a theory or description of executive functioning from studies that did not. The percentage of studies that used a theoretical description of executive functioning was 35.6 per cent (n=139).

**Figure 4.10**

*Constructs Used to Describe Executive Functioning and the Frequency of Use*



*Note:* The constructs and frequency of use presented in this graph has been extracted only from studies providing a theory or description of executive functioning (n=139).

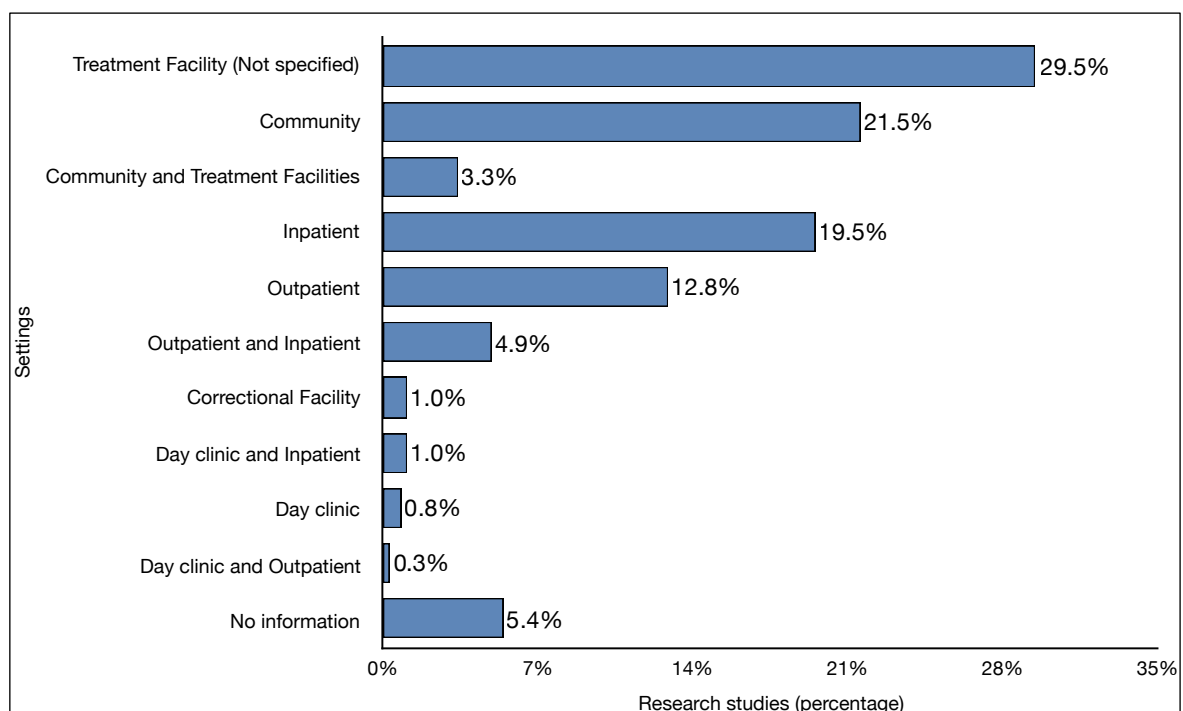
All the constructs used to describe executive functioning were extracted from the data tables and the frequency of use was calculated. A total of 36 constructs were extracted. Figure 4.10 presents the frequency with which each construct was used in all the studies that provided a description. The construct inhibition or its inverse, impulsivity, was used most often as a component to describe executive functioning (n=74, 53.2%). This is followed by planning, cognitive flexibility, and working memory which were used in 40 per cent of the studies.

#### 4.5.2 Settings

The dataset for settings was obtained from the recruitment procedures of population samples, excluding healthy controls. As presented in Figure 4.11, the majority of studies (68.7%, n=268) had population samples from a treatment facility setting.

**Figure 4.11**

*Percentage of Studies per Setting Category*



These included residential or hospitalised inpatients, outpatients with routine visits, day clinics where patients spent each evening at home, a combination with samples drawn from more than one type and finally, unspecified facilities. The variability, as calculated

using the index of qualitative variation, was 0.89 and revealed an unequal distribution on the categories for settings.

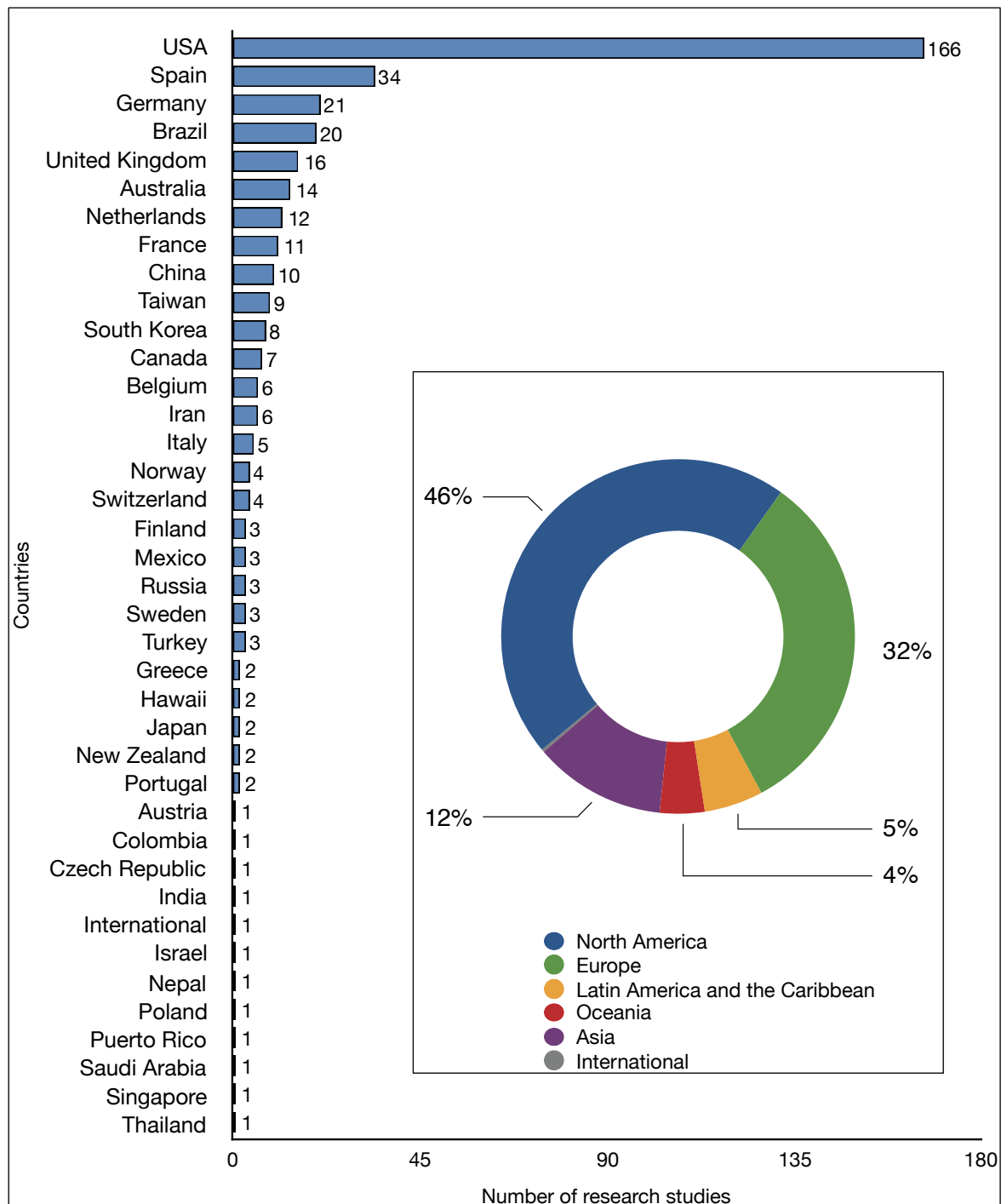
Eighty-eight studies (22.6%) drew samples from the community, including correctional facilities, which comprises individuals not explicitly reported as receiving treatment. There were also studies that recruited samples from both community and treatment settings (n=13). Twenty-one studies (5.4%) did not report recruitment procedures of samples; therefore, the settings for these studies could not be established.

#### **4.5.3 Countries**

As presented in Figure 4.12, the research studies were conducted in thirty-eight countries and one international study where population samples were recruited and participated via the internet. The largest number of studies (42.6%, n=166) originate from the United States of America, followed by Spain (8.7%, n=34), Germany (5.4%, n=21) and Brazil (5.1%, n=20). The countries were further categorised according to global region and this revealed that 46 per cent of the studies originate from North America, 32 per cent from Europe, 12 per cent from Asia and a minority from Oceania, Latin America and the Caribbean. There were no studies originating from Africa. The index of qualitative variation was used to calculate the variability score of 0.82. This revealed an unequal distribution between countries with research studies.

**Figure 4.12**

*The Number of Studies per Country and Percentage of Studies per Global Region*



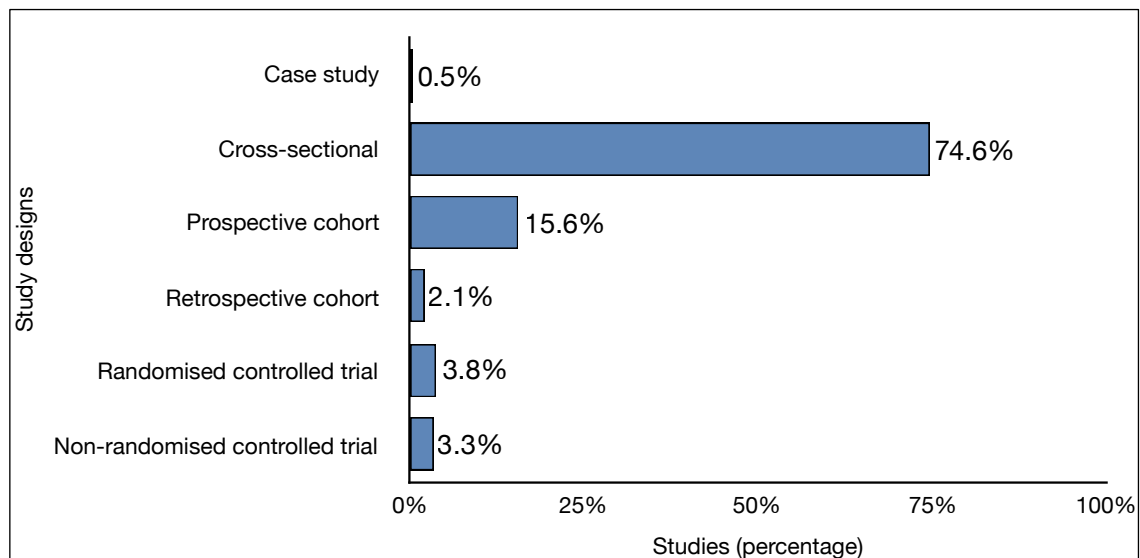
#### 4.5.4 Study Designs

Twenty-eight (7.2%) of the research studies were experimental, which included an intervention as part of the study design; and the majority, 362 (92.8%), were observational. The percentage of studies per study design is presented in Figure 4.13. The majority of

studies (n=291) had a cross-sectional design, primarily reporting on findings from a specific point in time. Sixty-nine studies had a cohort design, with studies observing changes over time either retrospectively (n=8) or prospectively (n=61). There were only two case studies. The variability score of 0.5 revealed a significant unequal distribution on the study design categories as calculated using the index of qualitative variation.

**Figure 4.13**

*Percentage of Studies per Study Design*



#### 4.5.5 Comparators

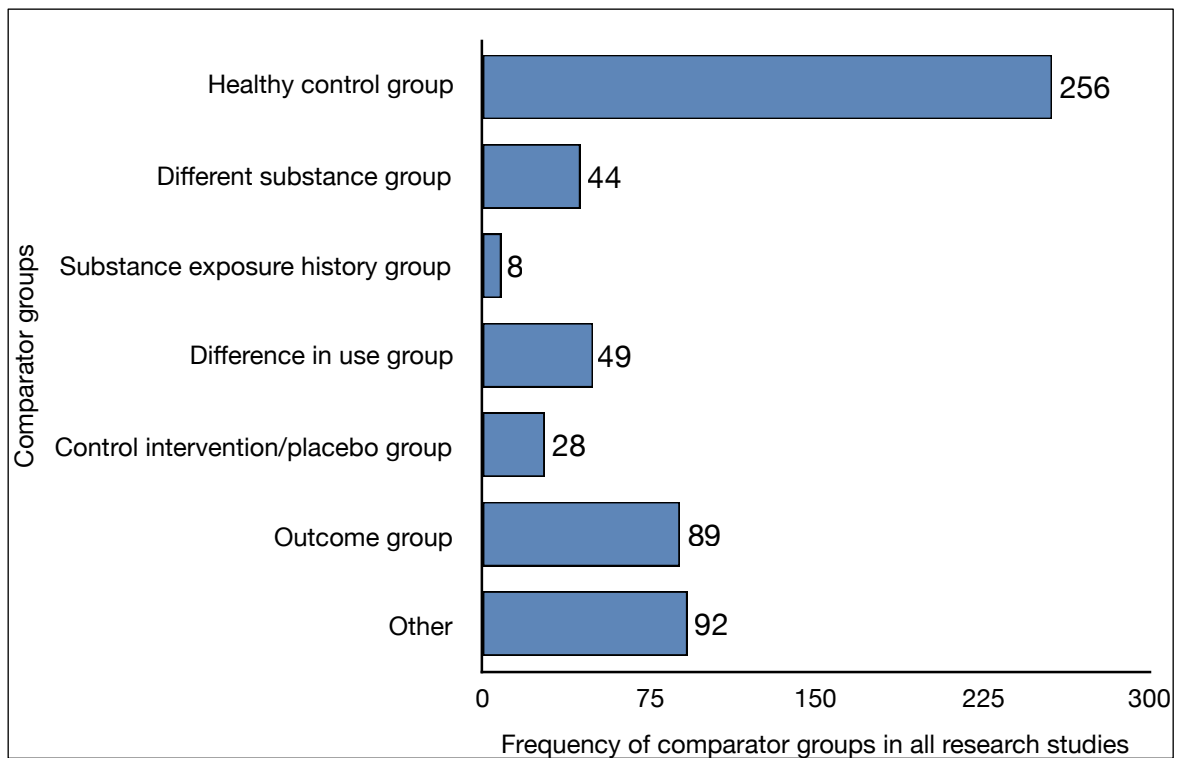
Healthy control groups were used in a large proportion of the studies (n=256, 65.6%). Control intervention or placebo groups were used in 28 studies (7.2%) and outcome groups in 89 studies (22.8%). Forty-four studies (11.3%) compared groups using different substances and 49 studies (12.6%) compared groups with differences in use. A small number of studies (n=8; 2%) compared groups in terms of exposure history. These results are presented in Figure 4.14.

There were ninety-two studies with additional atypical comparison groups that were combined as Other. These included various comparator groups that fall into different categories such as diagnoses, personality traits, gender, age, twin or sibling, family history and housing.



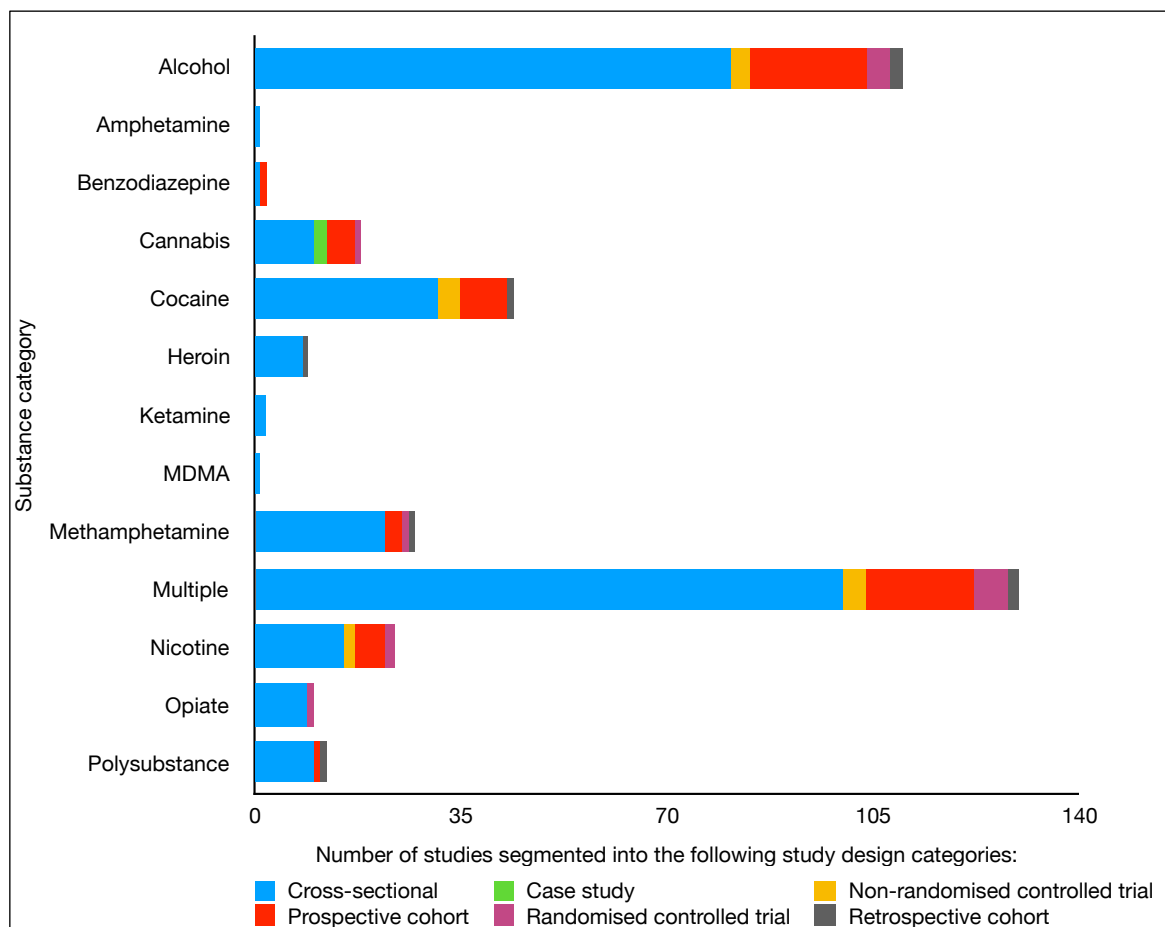
**Figure 4.14**

*Frequency of the Use of Various Comparators in the Research Studies*



#### **4.5.6 Study Designs in Terms of Substances**

The substance categories were cross-tabulated with the various study designs. From this it is evident that the majority of studies for all substance categories had a cross-sectional design. The only two case studies were for cannabis. There were no studies with a prospective or retrospective cohort design for opiates and only one study with a retrospective cohort design for heroin. These are presented in Figure 4.15 and the number of studies for each substance and study design is listed in Table 4.1.

**Figure 4.15***Proportion of Study Designs Used for Each Substance Category***Table 4.1***Number and Percentage of Studies According to Study Design and Substance Category*

Substance	Cross-sectional		Case study		Non-randomised controlled trial		Prospective cohort		Randomised controlled trial		Retrospective cohort	
Alcohol	81	20.77 %	-	-	3	0.77 %	20	5.13 %	4	1.03 %	2	0.51 %
Amphetamine	1	0.26 %	-	-	-	-	-	-	-	-	-	-
Benzodiazepine	1	0.26 %	-	-	-	-	1	0.26 %	-	-	-	-
Cannabis	10	2.56 %	2	0.51 %	0	-	5	20.77 %	1	0.26 %	-	-
Cocaine	31	7.95 %	-	-	4	1.03 %	8	2.05 %	-	-	1	0.26 %
Heroin	8	2.05 %	-	-	-	-	-	-	-	-	1	0.26 %
Ketamine	2	0.51 %	-	-	-	-	-	-	-	-	-	-
MDMA	1	0.26 %	-	-	-	-	-	-	-	-	-	-
Methamphetamine	22	5.64 %	-	-	-	-	3	0.77 %	1	0.26 %	1	0.26 %
Multiple	100	25.64 %	-	-	4	1.03 %	18	20.77 %	6	1.54 %	2	0.51 %

Nicotine	15	3.85 %	-	-	2	0.51 %	5	1.28 %	2	0.51 %	-	-
Opiate	9	2.31 %	-	-	-	-	-	-	1	0.26 %	-	-
Polysubstance	10	2.56 %	-	-	-	-	1	0.26 %	-	-	1	0.26 %

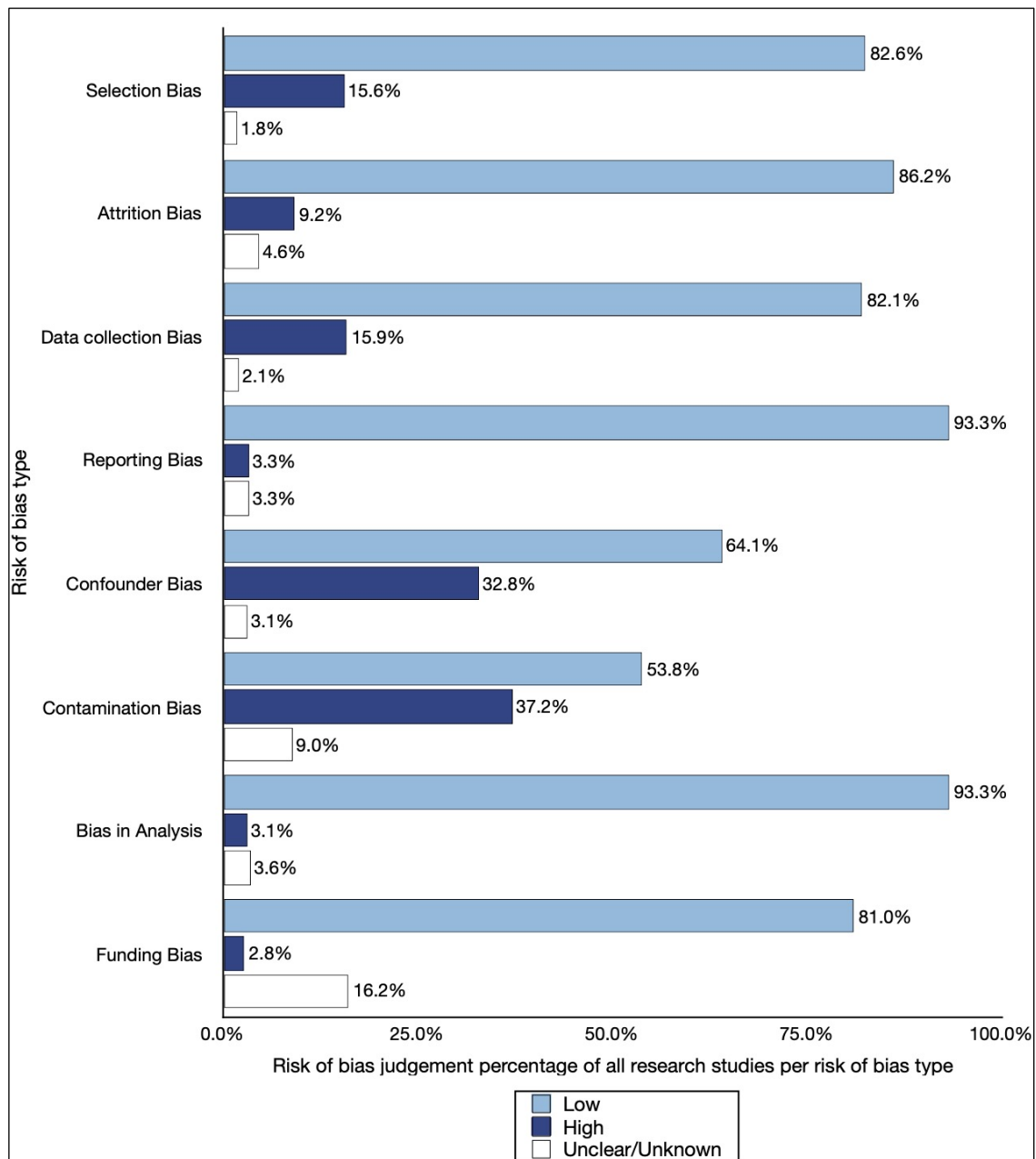
#### ***4.5.7 Risk of Bias and Limitations***

These results should be interpreted with caution as many of the judgments could be construed as a study limitation instead of a risk of bias. Therefore, it can be surmised that the risk of bias has been overestimated. A further discussion follows in Chapter 5. Even with an overestimation, the overall risk of bias of the research studies was low for all risk of bias types.

As presented in Figure 4.16, the risk of selection bias for the majority of research studies was low (n=322; 82.6%) compared to 61 studies (15.6%) judged as having a high risk. Eighty-six per cent (n=336) of the studies had a low risk of attrition bias in comparison to 9.2 per cent (n=36) with a high risk judgement. Sixty-two studies (15.9%) had a high risk of data collection bias and 320 (82.1%) had a low risk. A small number of studies had a high risk of reporting bias (n=13; 3.3%) and 364 studies (93.3%) had a low risk. The risk of confounder bias and contamination bias was judged high in a substantial number of studies. Confounder bias was judged as high in 128 studies (32.8%) and 250 studies (64.1%) were judged as low. The risk of contamination bias judgement was high in 145 studies (37.2%) and low in 210 studies (53.8%). Bias in analysis was low in 364 studies (93.3%) and high in 12 studies (3.1%). The number of studies were substantial (n=63; 16.2%) that did not report on funding or required more information to determine the risk of funding bias.

**Figure 4.16**

*Synthesised Ratings for the Research Studies per Risk of Bias Type*

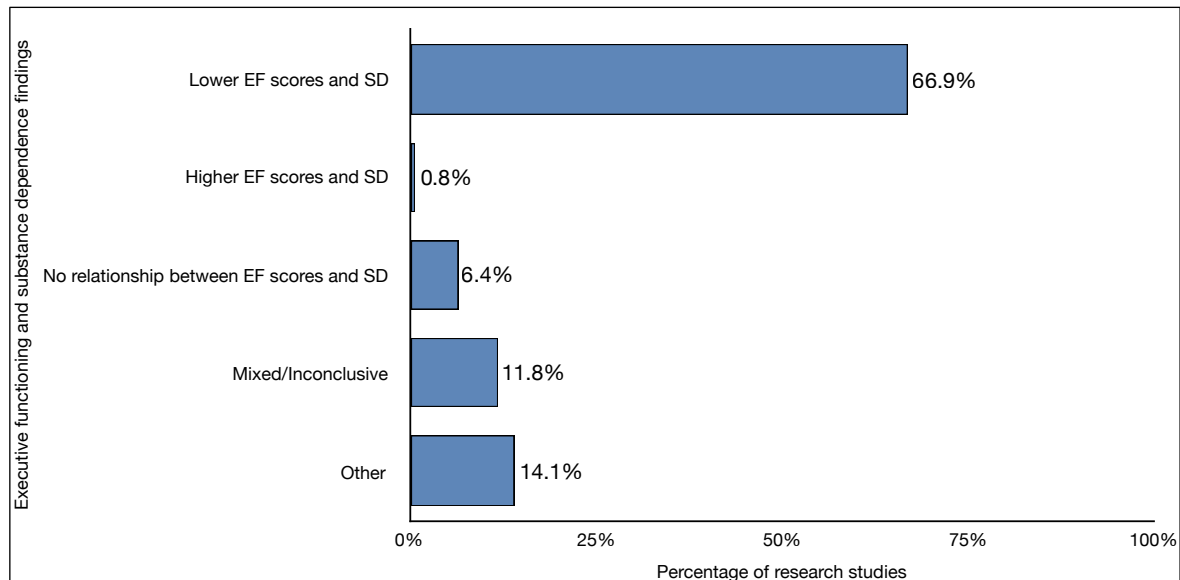


## 4.6 Findings of Studies

In terms of all the study and population characteristics presented thus far, it was anticipated that the reported results of the studies would also be highly heterogeneous. Therefore, the study results were analysed by locating the findings related to the relationship between executive functions and substance disorders in the extracted data of the respective studies and categorising these findings.

**Figure 4.17**

*The Percentage of Studies per Findings of the Relationship between Executive Functioning and Substance Dependence or Disorders*



*Note.* EF = Executive functioning. SD = Substance disorders/dependence.

The findings were categorised as reporting (1) a relationship between lower executive functioning scores and substance disorders ( $n=261$ , 66.9%); (2) a relationship between higher executive functioning scores and substance dependence ( $n=3$ , 0.8%); (3) no relationship between executive functioning scores and substance dependence ( $n=25$ , 6.4%); (4) mixed or inconclusive findings ( $n=46$ , 11.8%); and (5) other ( $n=55$ , 14.1%) which are included in the categories listed in Table 4.2. These categories are graphed in Figure 4.17. It is important to note that the categories refer specifically to executive functioning scores and not executive functioning abilities. This is to take into consideration the high variability in both the constructs used to define executive functioning (see Section 4.5.1) and the different assessment instruments used to measure these constructs (see Section 4.4.2).

The number of studies with other or additional findings are listed in Table 4.2. Thirty-six studies had findings about differences in neurophysiological morphometry or neurobiological markers related to executive functioning and substance dependence. The treatment group (where treatment was investigated) executive functioning scores was reported in 22 studies with 19 of these studies reporting a higher executive functioning

score in the treatment group. Two reported no differences and one reported lower scores in the treatment group.

**Table 4.2**

*Number of Studies with Other and Additional Findings Related to Executive Functioning and Substance Disorders*

<b>Variables</b>	<b>Number of studies</b>
Neurophysiology/neurobiology	36
Treatment group	22
Abstinence	18
Severity of use (general)	15
Comorbidity	11
Different substance type groups	9
Years of use	8
Treatment outcome	7
Early onset	5
Methadone maintenance	5
Neuropsychological instrument properties	5
Poor treatment outcome	5
Relapse group	5
Denial/Motivation/other trait	4
Personality disorders	4
Social cognition	4
Treatment drop-out	3
Abstinence (early)	2
Different methods of use	2
Emotional regulation	2
Gender differences	2
Specific neuropsychological instrument results	2
Adverse withdrawal	1
Chemical and behaviour	1
Childhood factors	1
Multiple confounders	1
Parental exposure	1
Polysubstance	1
Severity of use (dosage)	1
Severity of use (route of administration)	1
Social support	1
Unemployment	1

Seven studies had findings related to treatment outcome (where outcome was investigated) of which three reported executive functioning scores did not predict treatment outcome, one that executive functioning scores predicted treatment outcome, two reported a relationship between lower executive functioning scores and poorer treatment outcome and one reported no relationship was found between executive functioning scores and treatment outcome.

Eighteen studies had findings related to abstinence. Of these, eight reported on a relationship between abstinence and higher executive functioning scores; nine reported no relationship and one study had mixed results. There were also two studies that reported on early abstinence specifically, with both reporting a relationship between early abstinence and lower executive functioning scores. Findings related to the severity of substance use and executive functioning was reported in 17 studies, one of which provided results on the substance dosage and another on the substance route of administration. Sixteen of these studies reported lower executive functioning scores with an increased severity of use and one reported higher anhedonia with an increased severity of use.

Of the five studies that had findings related to methadone maintenance, three reported a relationship between methadone maintenance and lower executive functioning scores, one reported higher scores and one reported scores within the normal range.

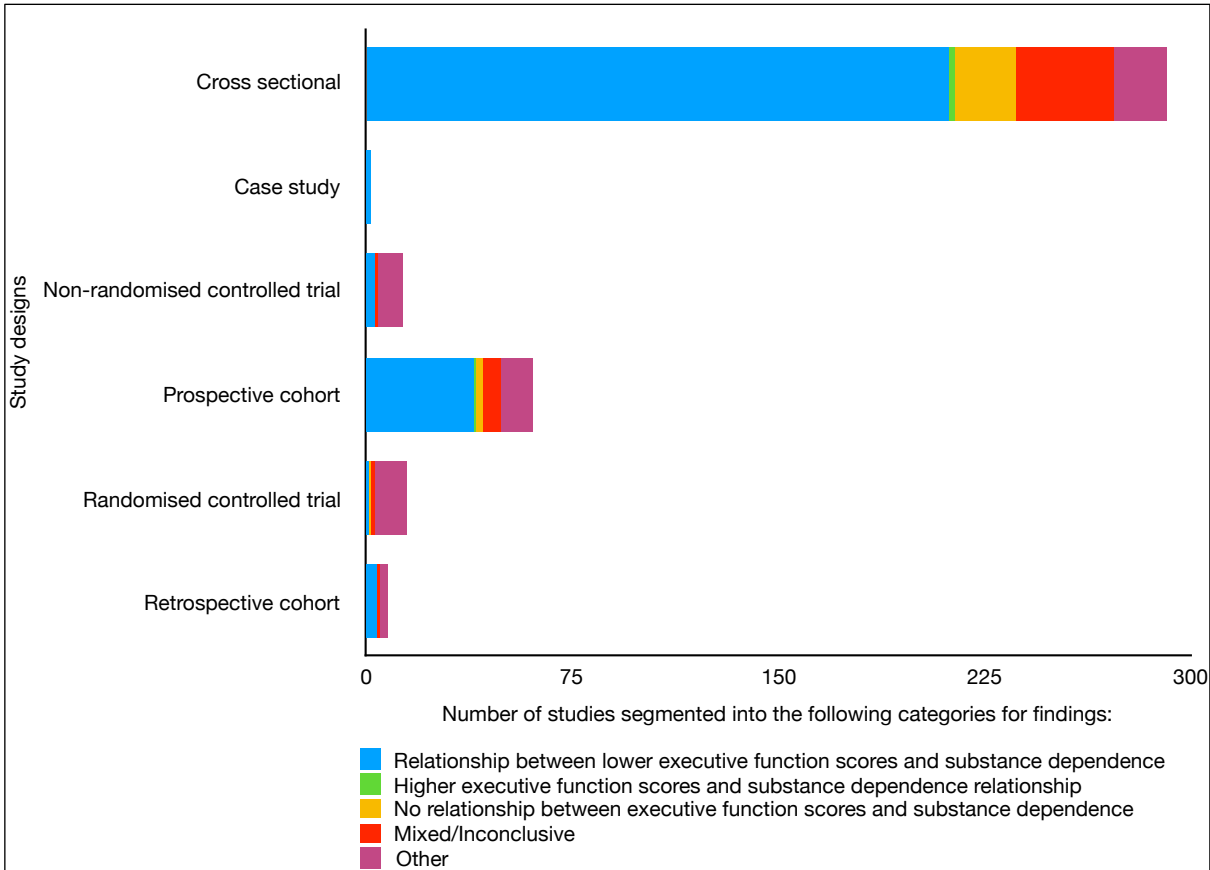
In terms of the years of education and findings, there were only 22 studies with samples that had an educational level of less than nine years. Of note, however, is that 77 per cent of these studies (n=17) reported lower executive functioning scores in substance dependent samples; in comparison to 71 per cent (n=97) of the studies with participants who had completed some secondary education; and 63 per cent (n=117) of the studies with participants who had 12 years of education or more.

#### ***4.6.1 Findings of Studies in Terms of Study Designs***

The findings and study designs were cross-tabulated and Figure 4.18 presents the proportion of findings for the various study designs. The majority of the studies with a cross-sectional design reported a relationship between lower executive function scores and substance dependence (n=212). However, a substantial number of cross-sectional studies had mixed or inconclusive results (n=36) and two reported a relationship between substance dependence and higher executive function scores. The studies with prospective cohort designs also had a majority of studies reporting a relationship between lower

executive function scores and substance dependence. The randomised and non-randomised controlled trials had mostly findings related to different treatment types and was categorised as *other*. Table 4.3 contains the number of studies for each study design and different findings.

**Figure 4.18**  
*Proportion of Findings for the Different Study Designs*





**Table 4.3***Number and Percentage of Studies According to Study Design and Findings*

	<b>Cross sectional</b>		<b>Case study</b>		<b>Non-randomised controlled trial</b>		<b>Prospective cohort</b>		<b>Randomised controlled trial</b>		<b>Retrospective cohort</b>	
Lower EF and SD	212	54.36 %	2	0.51 %	3	0.77 %	39	10 %	1	0.26 %	4	1.03 %
Higher EF and SD	2	0.51 %	-	-	-	-	1	0.26 %	-	-	-	-
No relationship EF and SD	22	5.64 %	-	-	-	-	2	0.51 %	1	0.26 %	-	-
Mixed/ Inconclusive	36	9.23 %	-	-	1	0.26 %	7	1.79 %	1	0.26 %	1	0.26 %
Other	19	4.87 %	-	-	9	2.31 %	12	3.08 %	12	3.08 %	3	0.77 %

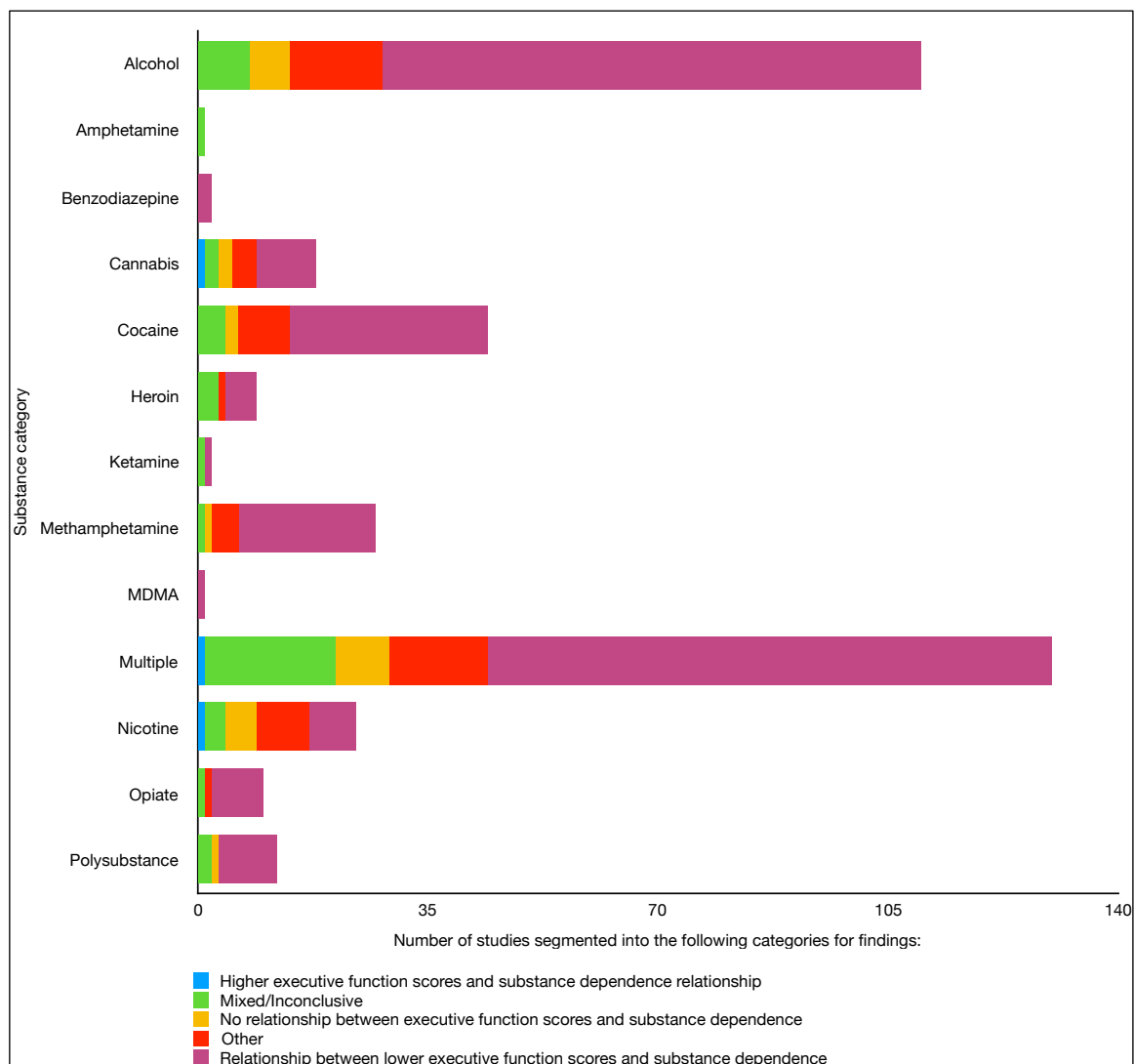
*Note.* EF = Executive functioning. SD = Substance disorders/dependence.

#### **4.6.2 Findings of Studies in Terms of Substances**

The substance categories and findings were cross-tabulated and the results are presented in Figure 4.19. Eighty-two of the studies investigating alcohol reported a relationship between lower executive functioning scores and substance dependence. Eight studies had mixed or inconclusive results and six reported no relationship could be found between executive functioning scores and substance dependence. For nicotine, seven studies reported a relationship between lower executive functioning scores and substance dependence, three had mixed results, five found no relationship and one reported higher executive functioning scores with substance dependence. The number of studies for each substance and findings category is listed in Table 4.4.

**Figure 4.19**

*Proportion of Findings for the Various Substance Categories*



**Table 4.4***Number and Percentage of Studies for Each Substance Category and Findings*

	<b>Alcohol</b>		<b>Amphetamine</b>		<b>Benzodiazepine</b>		<b>Cannabis</b>		<b>Cocaine</b>		<b>Heroin</b>		<b>Ketamine</b>	
Higher EF and SD	-	-	-	-	-	-	1	0.26 %	-	-	-	-	-	-
Mixed/ Inconclusive	8	2.05 %	1	0.26 %	-	-	2	0.51 %	4	1.03 %	3	0.77 %	1	2.05 %
No relationship EF and SD	6	1.54 %	-	-	-	-	2	0.51 %	2	0.51 %	-	-	-	-
Lower EF and SD	82	21.03 %	-	-	2	0.51 %	9	2.31 %	30	7.69 %	5	1.28 %	1	0.26 %
Other	14	3.59 %	-	-	-	-	4	1.03 %	8	2.05 %	1	0.26 %	-	-
	<b>Methamphetamine</b>		<b>MDMA</b>		<b>Multiple</b>		<b>Nicotine</b>		<b>Opiate</b>		<b>Polysubstance</b>			
Higher EF and SD	-	-	-	-	1	0.26 %	1	0.26 %	0		-	-		
Mixed/ Inconclusive	1	0.26 %	-	-	20	5.13 %	3	0.77 %	1	0.26 %	2	0.51 %		
No relationship EF and SD	1	0.26 %	-	-	8	2.05 %	5	1.28 %	-	-	1	0.26 %		
Lower EF and SD	21	5.38 %	1	0.26 %	86	22.05 %	7	1.79 %	8	2.05 %	9	2.31 %		
Other	4	1.03 %	-	-	15	3.85 %	8	2.05 %	1	0.26 %	-	-		

*Note.* EF = Executive functioning. SD = Substance disorders/dependence.

## **4.7 Conclusion**

In this chapter the findings of the systematic review were presented after synthesising the data from all the included research studies. The demographics of the population samples were depicted by providing an overview of the distribution and variation in terms of age groups, educational level, gender distribution, substance dependence and comorbidities. The various criteria used to determine substance use and dependence were described, as well as the numerous neuropsychological instruments to assess executive functioning. In terms of study characteristics, I presented the multitude of constructs used to define or describe executive functioning, the settings, the countries, the various study designs, and the different comparator sample groups used in the studies. Furthermore, the results from the risk of bias assessment of the research studies were delineated. Finally the results of the research studies related to executive functioning and substance dependence were synthesised. These synthesised findings were presented for all the studies, the various substance categories and the different study designs. The interpretation of the results in this chapter is discussed in Chapter 5.

## **Chapter 5: Discussion and Conclusions**

### **5.1 Introduction**

The main objectives of this systematic review were to identify the available empirical studies related to substance dependence and the neuropsychological assessment of executive functions, and to conduct a synthesis with the aim of delineating the current state of the existing body of knowledge and addressing the current state of fragmentation. To accomplish this, the following predefined review questions had to be answered: (1) Which substance dependent populations have been assessed using neuropsychological measures for executive functioning? (2) Which assessments and batteries were used to measure executive functioning? (3) What comparators were used in the respective studies? (4) What are the findings of the neuropsychological assessment measures? (5) In what settings were assessments conducted? (6) Which study designs were used? (7) What is the risk of bias within the respective studies? (8) What are the key consensus or near-consensus findings regarding the relationship between executive functions and substance dependence? (9) Are there any marked differences or inconsistencies between studies? (10) What are the strengths and limitations of the study designs that were used? (11) Are there any controversial issues? (12) Is exhaustive evidence provided or are there gaps and a need for further research?

In this chapter these questions are answered by discussing the results presented in Chapter 4. The main findings of the systematic review are discussed in terms of the demographics, substances, neuropsychological assessment measures, diagnostic criteria, study characteristics (theories, study designs, settings and countries) and findings. Thereafter, the strengths and limitations of the systematic review are discussed. Lastly, the identified gaps and implications of the findings are outlined, and a conclusion is provided.

### **5.2 Main Findings**

#### **5.2.1 *Demographics***

There were very few studies of adolescents and senior adults as most of the studies had samples aged between 30 and 50 years. Contrary to the latter, the observed trends for peak levels of substance use in most international regions and for most substances are observed among individuals aged between 18 and 25 years (United Nations Office on

Drugs and Crime, 2019). The majority of studies had samples with either completed or partially completed secondary education and only a small number of studies had samples with an education of less than nine years. In terms of the gender distribution of the studies, these are significantly uneven with the largest number of studies having a majority of males within the population samples. The uneven distribution of sample demographics of the included studies might be because of an uneven distribution existing in the various populations (United Nations Office on Drugs and Crime, 2017, 2019); however, it may also be because of various types of sampling bias (Wagner et al., 2012). The highly unique challenges faced by women with substance dependence, especially the various barriers to treatment access and a number of other social factors outlined by Tuchman (2010), should also be considered as possible reasons for the significant unequal distribution of gender in the samples of research studies. Furthermore, gender differences in terms of executive functioning and substance dependence are important because differences between the sexes in terms of neurophysiology and neurodevelopment have been demonstrated. Although, in general, the group differences in overall neuropsychological performance are less than half of a standard deviation (Mitrushina et al., 2005), fragmentation exists for specific domains such as executive functioning. Only a select number of the included studies investigated gender differences and this is clearly a significant weakness in the existing body of knowledge.

### **5.2.2 Substances**

When the studies were categorised per substance, one third of the studies investigated multiple substances which included samples using different substances. This is followed closely by alcohol. In terms of the number of substance samples within all the included studies, more than half of all the studies had alcohol dependent samples and a third had samples with cocaine disorders. Compared to the few studies investigating cannabis exclusively, there were more studies with cannabis dependent sub-groups. There were very few studies investigating the effects of dependence to amphetamine, benzodiazepine, heroine/opiates and ketamine on executive functioning, exclusively. This suggests that relatively little research has been done on the link between substance dependence and executive functioning for substances other than alcohol, cannabis and cocaine.

### **5.2.3 Neuropsychological Assessment Measures**

The Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT) and the Stroop Test were the most used instruments for executive functioning assessment. Overall, the frequency of instrument usage in the research studies corresponds to the reported assessment practices in neuropsychology (Rabin et al., 2005; Rabin et al., 2016; Strauss et al., 2006). The WCST is the most used instrument for executive functioning in these findings as well as in more general reported test-usage. The TMT and Stroop Test are also ranked within the top five of these reports. However, there are some noteworthy differences: The Delis–Kaplan Executive Function System (D-KEFS) is a useful battery for isolating and revealing underlying neurocognitive mechanisms and thereby reducing the persistent task impurity problem in neuropsychological assessment (Delis et al., 2004; Strauss et al., 2006). This battery was used in only twelve studies of the current systematic review and only a select number of modules of the battery was used; this contrasts with the latest report by Rabin et al. (2016) which ranks the use of this battery among the top five. Similarly, the Halstead Category Test is used in only eight studies, but is ranked among the top ten in the reported assessment practices. This test measures abstraction, concept formation, flexibility, novel problem solving and the ability to learn from experience. It is, therefore, evident why it ranks highly in instrument usage for the assessment of executive functioning, but it is unclear why so few of the included studies used this instrument. Speculatively, it may be because the Wisconsin Card Sorting Test measures the same constructs, the availability of the instrument or some other convenience factor, but it would be beneficial to investigate how the scores of these measures compare in substance dependence populations. The Behaviour Rating Inventory of Executive Function Adult (BRIEF-A) is also ranked among the top ten in the practice report but used in only nine of the included studies. The BRIEF-A is a specialised questionnaire in both a self-report and an informant report format. This is significant because it addresses the possible limitation of reporting bias observed in substance dependent populations and identifies different manifestations of executive dysfunction, especially pertaining to activities of daily living (which standard instruments do not measure). Finally, when intelligence and achievement instruments are accounted for, the current findings and the reported neuropsychological assessment practices correspond; the Wechsler Adult Intelligence Scale (various versions) is the most used of these instruments. Overall, these findings suggest that future studies on the relationship between substance dependence and executive functioning would do well to

more carefully consider the merits and demerits of available instruments such as the Halstead Category Test and to avoid choosing instruments on the basis of convenience.

#### ***5.2.4 Substance Use and Dependence Assessment Criteria***

More than half of the studies used the substance use and dependence criteria from the various versions of the Diagnostic and Statistical Manual of Mental Disorders. In comparison only a small percentage (6.7%) of the studies used the criteria from the International Statistical Classification of Diseases and Related Health Problems. Furthermore, another 34 different measures were used to establish substance use and dependence. Even though the criteria are similar, there are nonetheless differences, such as omitting specific criteria and thereby having broader inclusion criteria. This, in turn, increases the heterogeneity of the combined samples of the included studies.

#### ***5.2.5 Study Characteristics***

##### **5.2.5.1 Theories and Descriptions of Executive Functioning.**

Although a broad understanding of executive functioning exists, being a higher order or supervisory mental process, there is still no agreement about the constituent functions or lower order mental processes that make up this broad construct (Goldberg, 2017; Goldstein et al., 2014; Suchy et al., 2017). This was also evident when the constructs used to define executive functioning in the included research studies were extracted. The variability is high, as thirty-six different constructs were used to define executive functioning and the number of constructs used per study ranged between one and ten. This also indicates that the construct validity of executive functioning for the various studies may be low. This is of great concern as the neuropsychological instrument selection and subsequent results depend on the theoretical framework of executive functioning. As conceptualised by Suchy, Niermeyer and Ziemnik (2017), the possible theoretical frameworks for executive functioning can be classified into clinical models, cognitive models or developmental models; furthermore, the executive functioning measures can be categorised as clinical, experimental or self-report. Taking this into consideration, it is evident that it is essential to explicitly report the theoretical models used for research purposes. Yet, only 36 per cent of the included studies provided a description or definition of executive functioning. Furthermore, this fragmentation raises the question of whether it is valid to regard the studies as measuring the same neuropsychological construct.



#### **5.2.5.2 Study Designs.**

Three quarters of all the included studies had a cross-sectional design. Although cross-sectional designs can be easier to conduct than longitudinal designs, the main limitation for this study design is that causal inferences cannot be established. As already emphasised, in the fields of substance dependence and addiction there are numerous confounding variables which already lowers the confidence in both causality itself and the direction of causality in substance dependence and executive functioning. Therefore, longitudinal studies are of utmost importance and it is disappointing that so few have been conducted.

There were very few studies with a retrospective cohort design and only a select number of substances have been investigated in this way. A retrospective cohort design is important when investigating historical factors in substance dependent populations, for example age of onset, differences in use, differences in severity and other premorbid factors. However, this study design may be limited by the possibility of inaccurate medical history, especially when this is reliant on self-report data.

Where the studies with a retrospective cohort design obtain and analyse historical data leading up to a certain point in time, the studies with a prospective cohort design measure changes over time and report on a number of different outcomes. Specifically, if executive functioning scores predicted treatment outcomes, the likelihood of drop-out, successful abstinence, relapse, neurophysiological or biological changes, the likelihood of polysubstance use, the development of substance disorders and severity of use. Other studies reported if executive functioning scores improved with either abstinence or other variables such as social support. In brief, the investigated outcomes were found to be highly diverse for the studies using a prospective cohort design. The main limitation noted for both retrospective and prospective cohort design was the limited control of certain variables, for example the substance use or abstinence over the course of the research project, the accuracy of self-report data and the attrition rate.

The few studies with randomised and non-randomised controlled trials had diverse pharmacological and rehabilitation treatment interventions. Because of these diverse interventions the results from these studies cannot be combined and do not necessarily report specifically on the relationship between executive functioning scores and substance dependence. Nevertheless, combined with studies using a prospective cohort design, there

were noteworthy observations, especially related to methadone treatment. Some of these studies reported higher executive function scores with methadone treatment and others reported lower executive function scores. There were also a number of controlled trials investigating the effects of different cognitive training regimens on executive functioning with some promising findings.

Interestingly, there were only two case studies, and both of these were for cannabis (Crean, et al., 2011; Gonçalves et al., 2010). These studies provided expert opinions and specifics related to the patient history that are not necessarily evident in other research designs. This demonstrates that case studies may be valuable by providing substance-specific information as well as possible in-depth exploration of confounding variables.

In terms of the comparators used in the research studies, the majority of the studies used a healthy control group as a comparator. All the randomised and non-randomised control trials had groups receiving a controlled or placebo intervention. There were also a number of studies comparing groups that differ in the type of substance, the method of use, the dosage, or exposure history. Comparator groups may be an alternative for the lack of neuropsychological normative data for certain populations, possibly controlling for many other confounding variables not controlled for in normative data.

#### **5.2.5.3 Settings.**

The results for the various settings of the research studies show that the samples were drawn from both the community and various types of treatment facilities. There were also studies with samples comprising of individuals from community and different types of treatment facilities. This is noteworthy because individuals from different settings differ considerably in terms of a number of factors, including current substance use status, abstinence, withdrawal status and pharmacological treatment. For example, individuals from a treatment setting may be in a withdrawal state and receive psychotropic treatment, whereas individuals from a community setting may be under the influence of a substance at the time of testing. As discussed in Chapter 1, this variability in the patterns of substance use and treatment has been highlighted in previous systematic reviews (Cohen et al., 2017; Crean, Tapert, et al., 2011; Potvin et al., 2018; Stevens et al., 2014) and can be regarded as a significant confounding factor.

#### **5.2.5.4 Countries.**

Of all the included studies, 46 per cent originated from North America, 32 per cent originated from Europe and 12 per cent from Asia. Less than five per cent of the studies were conducted in Oceania, Latin America and the Caribbean. The most conspicuous is that there were no studies from any African country. This geographical bias mirrors that found in much scientific research and is a significant concern with regard to the international applicability of findings.

#### **5.2.5.5 Risk of Bias.**

As discussed in Chapter 4, the risk of bias for the studies may have been overestimated as many of the judgements could be regarded as limitations rather than introduced bias. A third of the studies were judged as having a high risk of bias for confounders and contamination. The reason for these judgements is because the status of substance use, abstinence, withdrawal or psychotropic treatment was questionable and, in many studies, not reported at all. However, it is difficult and, in some cases, impossible to control these factors and therefore it may be regarded as a limitation. Although omitted information was not judged as a risk of bias, it remains of great concern, especially when considering that six studies had no information about the ages of the samples, 46 studies did not report the education level, 23 studies did not report the gender proportions of the samples, 24 studies did not report the criteria used to determine substance use or dependence, and 21 studies did not report the settings where samples were recruited from.

### ***5.2.6 Executive Functioning and Substance Dependence Findings***

The included research studies are highly heterogenous and therefore a meta-analytic synthesis of the extracted data for the results would not be valid. This was anticipated in the protocol and subsequently confirmed when study selection was completed. Therefore, it was clear a narrative synthesis was required for the results; however, to conduct a narrative synthesis it is also required for the results of the individual research studies to be combined to present the overall findings. This was done in three ways. First, the main results related to executive functioning scores and substance disorders or dependence were located, synthesised and these combined findings were reported. This provided an overview of the combined results for all 390 of the included research studies. Second, these findings were then cross-tabulated with the various substances to provide an overview of the combined results for the respective substances

that were investigated. Finally, the findings were cross-tabulated with the different study designs to give an overview of the combined results for the study designs.

As already outlined in this chapter, it is important to consider the caveats in both the demographics of the population samples and the various components of the studies when interpreting the synthesised results. In section 5.4.8, I provide recommendations to address these limitations. Nonetheless, these synthesised results provide a general overview, indicate possible gaps and can be used to guide future research.

Two thirds of the studies reported a relationship between lower executive functioning scores and substance dependence. Although this is a large proportion, the number of studies reporting mixed, inconclusive and no relationship remain substantial. The three studies reporting higher executive functioning scores with substance dependence are controversial, but may be important. Even though certain confounders may have had an impact on these results, the reported findings are curious. For instance, one of the included studies (Coulston, et al., 2007) reported that a schizophrenia group with lifetime cannabis abuse/dependence demonstrated better performance predominantly in the domains of attention, processing speed and executive functions in comparison to a schizophrenia group without this lifetime abuse/dependence. This was further associated with the frequency and recency of cannabis use. Although there are a number of other studies in this review that conversely reported lower executive function scores in schizophrenia populations, the quality and transparency of this particular study prompted further inquiry. With scoping searches (González-Pinto et al., 2016; Hanna et al., 2016; Jockers-Scherübl et al., 2007; Moustafa et al., 2016) it was confirmed that the cannabis-cognition-psychosis relationship may not fit in with the conventional brain-disease model or neurodevelopmental model of addiction. Clearly, this is an area of investigation that needs to be pursued further.

It can therefore be surmised from these synthesised findings that the existing body of research for executive functioning in substance dependence does not provide exhaustive evidence and a number of gaps have been identified. Before these gaps and recommendations for future research are discussed in section 5.4, the strengths and limitations of the systematic review should be considered.

### 5.3 Strengths and Limitations of the Systematic Review

A crucial requirement for any systematic review is the adherence to the predefined protocol (see Appendix A). The protocol guided the research project and every effort was made to follow the predefined criteria. However, certain deviations were necessary. A number of terms and word stems listed in the protocol resulted in an unmanageably large number of search results. For this reason, the search strategy was refined to ensure specificity (where relevant evidence is identified) and sensitivity (where irrelevant evidence is minimised). In conjunction, the list of databases in the protocol was also refined to ensure specificity and sensitivity. Even with a refined search strategy, the final number of search results was higher than anticipated (n=16 265) and cross-referencing the individual results with results from previous systematic reviews was not practical. Nonetheless, the search strategy did include citation chaining of previous systematic reviews with additional snowball citation chaining (see section 3.3.3).

Population inclusion criteria was formulated in the protocol to include human populations; diagnosed with substance dependence; or diagnosed with substance use disorder; or no diagnosis with recurrent use of psychoactive substances. The latter, however, was found to be too ambiguous when piloting the screening and was removed as an inclusion criterion. This ensured all included studies had samples with a reported diagnosis of addiction, substance-use disorder or substance dependence. All other inclusion and exclusion criteria were used exactly as defined in the protocol by both reviewers. Differences and consensus were not reported to the supervisor to monitor bias. This was because the agreement between the two reviewers was higher than the stipulated statistical requirements. Screening and selection of titles/abstracts and full-text articles were done in duplicate; however, the second reviewer screened and selected a sample of the studies and not all of the studies as proposed. This is an acceptable standard for conducting systematic reviews if the agreement between reviewers is high and in this case the agreement was higher than the required kappa score of 0.8 for both the titles/abstracts and the full-texts.

As discussed in Chapter 3, there were a number of full-text articles not available for screening despite efforts of requesting these articles from the university library and contacting the authors directly. Furthermore, a few articles were not available in English. It was proposed that these articles would be submitted to Cochrane Task Exchange for

translation; however, this was not feasible in terms of the timeframes and the English versions were requested from the authors directly. These included titles and abstracts with unavailable full-text articles are publicly available at DOI: [10.13140/RG.2.2.14658.32962](https://doi.org/10.13140/RG.2.2.14658.32962).

The protocol specified that *Covidence* would also be used for data extraction but because the software module was not as customisable as anticipated it was decided to use *Google Forms* instead. This meant that the extracted data were not highlighted in the specific article PDF documents as proposed in the protocol. Furthermore, each reviewer extracted data for a proportion of the studies and, therefore, data extraction was not done in duplicate. All other criteria for data extraction were followed as proposed.

Quality assessment was not carried out after data extraction because it was established during the course of the review that the reviewer is most familiar with each individual study directly after data extraction and, therefore, better able to make appropriate judgements, as opposed to a separate process of screening each article and then making judgements. Because of the customisability issues of *Covidence*, the quality assessment was also conducted on *Google Forms*. All other criteria for quality assessment were followed as proposed. The analysis of the extracted data was carried out exactly as described in the protocol.

The main limitations of the current systematic review are therefore: (1) The deviations from the predefined protocol which may have introduced bias; (2) Data extraction was not executed in duplicate which may have introduced bias; (3) The risk of bias for the individual studies may have been overestimated; (4) There were a number of full-text articles that could not be obtained for screening. The strengths of the systematic review are as follows: (1) A comprehensive, transparent and rigorous search strategy; (2) The use of both electronic databases and citation chaining for searches; (3) Blinded screening and selection which minimised bias; (4) The availability of comprehensive and detailed data for the use in subsequent research.

## **5.4 Identified Gaps and Implications for Future Research**

A heuristic of the synthesised components of the available 390 empirical studies reveals a middle-aged individual of the male gender, who completed secondary education (partially or in full) and is a citizen of the United States of America. He is diagnosed with substance dependence or substance-use disorder for either alcohol, cocaine or cannabis using the DSM-IV criteria and is currently receiving pharmacological and/or rehabilitative

treatment. His executive functioning is assessed on a single occasion, using the Wisconsin Card Sorting Test, the Stroop Test, and/or the Trail-Making Test. The assessment results indicate that he has lower executive functioning scores in comparison to healthy individuals without substance dependence and who have the same demographics as him. This heuristic view of the results clearly demonstrates the considerable restrictions of the existing body of knowledge for the neuropsychology of executive functioning and substance dependence.

#### **5.4.1 Demographics**

There is a lack of empirical studies that investigate the effects of substance dependence on executive functioning in both adolescent and senior-adult populations. This lack of research for both of these age groups is significant, especially when considering the well-known vulnerability of the developing adolescent brain (Arain et al., 2013; Griffin, 2017) and the prevalence of neurodegenerative diseases among senior populations, globally (Béjot & Yaffe, 2019; Hou et al., 2019; Johnson, 2015).

Future research studies need to include more female participants. This is supported by the *World Drug Report 2019* (United Nations Office on Drugs and Crime, 2019) which explains that substance-use research, in general, has predominantly used male participants; and consequently resulted in male-oriented substance-use interventions. Furthermore, the critical need to develop effective treatments tailored to the specific needs of women has been emphasised by world leading organisations (Arpa, 2017; National Institute on Drug Abuse, 2018) and to do this, any research pertaining to substance-use needs to include more female participants.

Education has a pervasive and potent effect on neuropsychological assessment performance (Lezak et al., 2012). In line with this, cross-tabulation of the educational years and the findings of the combined studies revealed that the samples that had less than secondary education had lower executive functioning scores in comparison to the samples who had some secondary education, and even lower than the samples with full secondary education or more. However, only a small number of studies had samples with less than nine years of education and, therefore, the specific relationship between educational level and executive functioning performance in substance dependent populations remains unclear. If a lower educational level is associated with lower executive functioning it may be considered an aggravating factor in substance dependence and more research is

therefore crucial. This is further supported by the fact that, globally, one in five people are excluded from education (UNESCO Institute of Statistics, 2018).

#### **5.4.2 Substances**

Very little research is available that investigates the relationship between executive functioning and dependence to ketamine, amphetamine and benzodiazepine.

The very small number of research studies with ketamine dependent samples is particularly alarming because epidemiological research indicates that prevalence has increased in many countries (McCambridge, Winstock et al., 2006; World Health Organization, 2012). Furthermore, none of these studies investigated the relationship between ketamine dependence and executive functioning longitudinally; nonetheless, ketamine is now being used internationally as a novel treatment for depression (Bratsos & Saleh, 2019; Grady et al., 2017; Strong & Kabbaj, 2018). In the 1990s, specific pharmacological treatment was introduced for pain management and reported as being safe. This was done without sufficient research for the associated risks (including the progressive addictive risk of the treatment) and resulted in a catastrophic epidemic, today known as the opioid crisis (DeWeerd, 2019; Van Zee, 2009).

Benzodiazepine is another prescription drug with potential long-term risks. This sedative may be associated with neurofunctional impairments and its potential to increase the risk of developing neurodegenerative diseases is being researched extensively (Brandt & Leong, 2017; De Gage et al., 2014; Richardson et al., 2019). Contrary to the latter, the effects of benzodiazepine dependence on executive functioning has not received much attention. Likewise, the lack of studies for amphetamines and prescription stimulants are also of great concern, especially when considering the global statistics of 29 million users, which is equivalent to the number of opiate users (United Nations Office on Drugs and Crime, 2019). Opioids are considered to result in the greatest harm to the health of individuals and accounted for 66 per cent of deaths due to drug-related disorders. Fifty-three million people use opioids (opiates and prescription opioids) globally. Yet, this is also a substance with little research pertaining to dependence and executive functioning.

Finally, the most commonly used illegal drug, as well as the primary drug of concern for people in treatment, is cannabis (United Nations Office on Drugs and Crime, 2017, 2019). Almost 4 per cent of the global population or 188 million people use cannabis. Furthermore, cannabis is the primary drug of concern for between 29 and 56 per cent of



the global population in treatment. This is significantly higher (globally ranging between 43 and 83 per cent) in persons younger than 20 years of age (Siphokazi et al., 2018; United Nations Office on Drugs and Crime, 2019). These statistics are critical, especially the extreme prevalence in adolescent populations who are most vulnerable in terms of neurodevelopment. Greater emphasis needs to be placed on investigating the relationship between cannabis dependence and executive functioning.

#### **5.4.3 *Assessment Measures***

In terms of neuropsychological assessment instruments, more research is required for particular neuropsychological instruments that assess the executive functioning in substance dependence populations, specifically (1) the Delis-Kaplan Executive Function System, (2) the Behavior Rating Inventory of Executive Function, and (3) the Halstead Category Test. In addition to the primary objective of more research to establish the relationship between executive functioning and substance dependence, more studies are also required to investigate the validity and reliability of these instruments. As discussed in Chapter 2, future research should also place an emphasis on cultural-sensitivity with neuropsychological assessment and ensure assessment is adapted for non-Western cultures (Ardila, 2005; Greenfield, 1997; Rosselli & Ardila, 2003).

#### **5.4.4 *Study Designs***

It is of major concern that the overwhelming majority of studies were cross-sectional in nature. Overall, additional longitudinal studies are required, but considering the diverse outcomes of the existing prospective cohort designs, more longitudinal studies are required in particular that investigate executive functioning and (1) treatment outcomes; (2) the likelihood of treatment drop-out; (3) success rate of abstinence; (4) likelihood of relapse; (5) neurophysiological or biological changes; (6) likelihood of polysubstance use; (7) the development of substance disorders; (8) and the severity of use. Furthermore, there is a lack of longitudinal studies investigating whether executive functioning scores improve with abstinence for the various substances. Of importance, and in conjunction with the relatively small number of studies for the adolescent group already mentioned, is the lack of longitudinal studies investigating the effect of early-onset substance dependence on executive functioning. As presented in the literature review, research emphasises the vulnerability of the developing adolescent brain, especially the prefrontal cortex which is directly associated with executive functioning (Arain et al.,

2013; Griffin, 2017). This has potentially significant implications for substance dependence and addiction.

While it makes intuitive sense that there is a relationship between executive functioning and substance dependence, this has very seldom been tested in controlled trials. From the systematic review it would appear that the relationship is much less commonly detected in such trials than in correlational studies, casting further doubt on the robustness of the relationship. In terms of studies that researched treatment, the findings in the various controlled trials that investigated the effects of methadone maintenance on executive functioning are conflicting and more research is required to establish consensus. Moreover, the few studies that investigated the effects of cognitive training on executive functioning for the treatment of substance dependence had promising findings which also supports the need for more research.

#### **5.4.5 Settings**

Future empirical studies need to control for the settings of participant recruitment more stringently. The diversity in settings is a significant confounding variable in terms of substance use behaviours and other factors (for example, the effects of treatment or withdrawal). Furthermore, the majority of studies recruited participants from treatment settings. This is not representative of the global population, as only one in seven people with substance dependence receive treatment (United Nations Office on Drugs and Crime, 2019). The effects of substance dependence on executive in populations from other settings may differ in populations from treatment settings.

#### **5.4.6 Countries**

The significant lack of research in certain global regions is concerning, especially when epidemiological statistics from the United Nations Office on Drugs and Crime (2017) are considered. Although substance dependence prevalence is not presented specifically in the latter report, it can be inferred from both the data about population numbers in treatment and drug-related deaths, that all global regions are detrimentally affected by substance dependence. To clarify, the majority of research included in this systematic review originates from North America and the estimated number of drug-related deaths for this region, as reported in 2015, is almost 60 000. In comparison, almost 70 000 drug-related deaths are reported for Asia and more than 40 000 for Africa. These statistics exacerbate the possible impact of the critical lack of research for Asia and non-

existent research for Africa. The latter may be, at least in part, attributed to the internationally recognised need for culturally-adapted neuropsychological assessment (Arango-Lasprilla et al., 2016; Bender et al., 2010; Rivera Mindt et al., 2010; Sue & Chang, 2003; Watts & Shuttleworth-Edwards, 2016). Furthermore, when cultural sensitivity is considered (as discussed in Chapter 2) it is not valid, nor ethical, to use the findings from research conducted in one culture to make inferences about another culture (Lezak et al., 2012). Therefore, based on the results of this systematic review, the relationship between executive functioning and substance dependence for populations in these regions remain unknown. Neuropsychological assessment instruments need to be culturally-adapted and normative data collected for research to be conducted in non-Western global regions.

#### ***5.4.7 Executive Functioning and Substance Dependence Findings***

Although the synthesis of findings confirmed lower executive functioning performance scores are commonly observed in substance dependence, studies need to be replicated to identify the specific impact of confounders as well as investigate the reasons for outlier empirical studies. For example, the higher executive functioning scores reported with cannabis dependence in schizophrenia populations. In addition, these findings are primarily from cross-sectional studies and longitudinal studies could provide a better understanding of the relationship between executive functioning and substance dependence. Particularly where these longitudinal studies investigate, for example, premorbid functioning, disease progression and abstinence.

#### ***5.4.8 Current Systematic Review as Basis for Future Research***

The included studies of this systematic review can be used to conduct a number of different meta-analytic systematic reviews. This can be done according to specific substances and/or specific study designs. The lower heterogeneity and synthesis of statistical power would provide high quality evidence. Similarly, the lack of research for gender differences can possibly be addressed by using refined inclusion criteria and conducting the appropriate meta-analyses. Furthermore, the data from the included studies can be used for comparative analyses of the scores from any combination of the neuropsychological assessment instruments. For example, how The Wisconsin Card Sorting Test and Halstead Category Test scores compare as instruments measuring the same constructs; or how the scores of the Behavior Rating Inventory of Executive

Function, and other instruments sensitive to the activities of daily living, compare with standard neuropsychological instruments.

Finally, the myriad of constructs used to describe executive functioning confirm the persistent lack of consensus. It is important to advance the field by increasing our understanding of executive functioning. This may be addressed by conducting factor analytical research. In addition, and as shown in the current systematic review, it may be possible to establish the various constructs used in multiple studies and then, using the combined data from these studies, conduct the appropriate factor analyses. Essentially, this will entail combining systematic review and factor analytical methodologies.

## **5.5 Conclusions**

The synthesis of the existing empirical studies related to executive functions and substance dependence confirmed that a relationship exists between these two constructs as is predicted by theoretical models of addiction. However, the synthesis of the various components of these studies revealed a number of critical gaps in the available research. This is most apparent in the discovery that the current body of knowledge is restricted in terms of the population it represents, especially with regard to gender, age, education and nationality; as well as the limited number of longitudinal studies and studies for specific substances of dependence known to be of epidemic proportions. The extent of fragmentation of executive functioning as a theoretical construct was revealed as another concern, and this fragmentation is further amplified by the multitude and diverse combinations of neuropsychological assessment instruments that were used to assess executive functioning. Based on these identified gaps, a number of recommendations were made, including the need for additional replication studies, meta-analytical systematic reviews and factor-analytical studies.

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# Appendices

## Appendix A: Protocol

### **Abridged Protocol: Neuropsychological Assessment of Executive Functions in Substance Dependence Populations: A Systematic Review**

#### **Statement of intent**

A thorough review of the existing empirical studies is needed to provide informative, evidence-based answers. Therefore, a systematic review is proposed to appraise existing studies and inform future research. The findings may improve our understanding of the neuropsychological effects of substance dependence and thereby contribute to improved mental healthcare for this population.

SAGE Publications Ltd (2017) describes this methodology as locating, evaluating and synthesising the best available evidence related to the research questions.

Numerous systematic reviews have been conducted that answer questions related to substance dependence and neuropsychological assessment. The scope of these reviews, however, are narrowed to either a specific substance; polysubstance use with a specific combination of substances; comorbidity with a specific condition as an additional construct of the study; the assessment of general cognition with some components of executive functioning; or the assessment of only a specific subdomain of executive functioning.

There is not a systematic review that includes all possible types of used substances and the neuropsychological assessment of executive functioning.

The existing literature needs to be searched and the appropriate data needs to be extracted and synthesised to answer the following review questions:

- Which substance dependent populations have been assessed using neuropsychological measures for executive functioning?
- Which assessments and batteries were used to measure executive functioning?
- What comparators were used in the respective studies?
- What are the findings of the neuropsychological assessment measures?
- In what settings were assessments conducted?
- Which study designs were used?
- What is the risk of bias within the respective studies?
- What are the strengths and limitations of the study designs?
- What are the key consensus or near-consensus findings regarding the relationship between executive functions and substance dependence?
- Are there any marked differences or inconsistencies between studies?
- Are there any controversial issues?
- Is exhaustive evidence provided or are there gaps and need for further research?

#### **Methods**

##### ***Protocol***

For a systematic review to adhere to the rigour and transparency of scientific inquiry, it is required to develop a protocol with an explicit, predefined methodology. All attempts will be made to follow the protocol throughout the review process and adequate reasons will be provided if the protocol is not followed in any way.

##### ***Literature search***

In order to conduct a literature search for a systematic review, an exhaustive list of key search terms is required to ensure the highest probability of locating all relevant studies (Gough, Oliver, & Thomas, 2012). After consultation with an information scientist, the search terms (Table 1) were collated through scoping searches, citation chaining and referencing. Three comprehensive glossaries were consulted for terms related to substance dependence (Australian Drug Information Network, 2016;

National Institute on Drug Abuse, 2016; The National Center on Addiction and Substance Abuse, 2017). Most of the substances have several commercial and street names and these may be varied from country to country. It is improbable that a study title and abstract will contain the street name or commercial name of a substance, exclusively. Therefore, only the most commonly recognised of these names were included in the search term list. All the internationally recognised terms for the substances were included in the list. The compendium of tests compiled by Lezak (2012) was consulted to obtain search terms for the neuropsychological assessment of executive functions. There are many tests and batteries used when assessing executive functions. Most of these, however, do not test executive functions exclusively and can be used to assess a myriad of other constructs. There are certain tests that are most frequently used in the assessment of executive functions, and these have been included in the search term list. Furthermore, the appropriate databases are listed in Table 2 (Boland, Cherry, & Dickson, 2017; Ndhlovu, 2018). The list contains databases which cover the scope of the proposed systematic review – the primary disciplines of psychology, neuroscience and addiction medicine. This includes international, general academic, medical, psychological and clinical research databases.

**Table 1:** List of search terms

Substance terms			Neuropsychological terms
Addiction	Mescaline	AND	Attention*
Alcohol*	Methadone		BRIEF Executive function*
Amphetamine	Methamphetamine		Cambridge Gambling
Amyl*	Methyl*		Card Sorting
Analgesic*	Morphine		Cognit*
Angel dust	Narcotic*		Decision making
Anxiolytic	Nitrous oxide		Digit span
AOD	nyaope		Executive function*
ATS	Opiate		Iowa Gambling
Barbiturate	Opioid		Neurocog*
Bath salts	Oxycodone		Neuropsych*
Benzodia*	Parameth*		Stroop
Caffeine	PCP		Tinkertoy
Cannabi*	Phencyclidine		Tower
Catha*	PMA		Trail Making
Cocaine	PMMA		Working memory
Codeine	Polydrug		
Crack	Polysubstance		
dependence	Propofol		
Dextromethorphan	Psilocybin		
Diaze*	Psychedelic		
Drug depend*	Psychoactive		
DXM	Psychostimulant		
Ecstasy	PWID		
Flunitrazepam	Rohypnol		
Gammahydroxybut*	Salvia		
GHB	Sedative		
Hallucinogen	Solvents		
Hallucinogen*	Speed		
Hash*	Spice		
Heroin	Steroid		
Hypnotic	Stimulants		
Inhalant	Substance		
Injection drug use	Substance abuse		
K2	Substance misuse		
Kava	Substance use		

Ketamine	Synthetic drugs		
Khat	tetrahydrocannabinol		
Kronic	THC		
LSD	Tobacco		
Lysergic acid	Tranquilliser		
Marijuana	Valium		
MDMA	Volatile substance		
Mephedrone			
* indicates the use of word stems			

**Table 2:** List of subject databases

Academic Search Premier	PsycEXTRA
Africa-Wide Information	PsycINFO
CINAHL Plus with Full-Text	PsycTESTS
Cochrane Library	PsychiatryOnline
CORDIS	Pubmed
ISAP	SA ePublications
JSTOR	Sage Journals Online
MEDLINE	ScienceDirect
Proquest	Taylor and Francis Online Journals
PsycARTICLES	Wiley Online Library

A full search will be conducted and all search activities will be recorded electronically. This will include the date and time, the database name and version, and the search syntax.

The following procedure will be followed for each search:

1. Each database will be searched with the search terms using Boolean logic.
2. Search results will be imported to Mendeley (including search record information).
3. Search results will be exported from Mendeley to Covidence in RIS format (Research Information Systems), which is a format used in both programs.

All search records will be screened to ensure it contains both a title and abstract. Missing information will be obtained by other means (for example, searching the specific journal entry) and the record will be updated manually.

Citation chaining will be performed after all the searches are completed. Using Microsoft Excel, the search results will be cross-referenced with the included studies of previous systematic reviews related to substance dependence and neuropsychological functioning. If any additional studies are found, these will be imported to Mendeley and Covidence with separate search record information. This strategy will also indicate how exhaustive the initial search strategy was. It is, however, anticipated that the initial search strategy will be exhaustive. If this is not the case, it will be necessary to identify search terms that were missed and use these to search all the databases.

### ***Screening and selection***

The results of all searches are combined in Covidence and any duplicates will be merged in the software.

To screen and select studies from the search results, it is necessary to have clear inclusion and exclusion criteria. This has been framed in terms of populations, interventions, comparators, outcomes, settings, study designs, languages, periods and ethics (Table 3).

As an overview, studies will be included where the populations are human, presenting with substance dependence and neuropsychological assessment of executive functions was administered. Studies with only animal models, neurocomputational models and other addictions will be excluded (for example, gambling or internet gaming). Studies where other instruments were used exclusively, such as neuroimaging, biochemical or genetic methods will also be excluded.

Studies will be included with or without comparators. For example, the comparison between a treatment group and a control group; or the comparison between a treatment condition and a control condition.

The measured outcomes of studies can be very different and therefore studies with any reported outcomes will be included. These may be, for example, related to adherence and relapse or the results of the neuropsychological assessment.

**Table 3: Inclusion and exclusion criteria**

Review Scope	Executive functioning assessment of substance dependence individuals	
	Inclusion criteria	Exclusion criteria
<b>Population</b>	Human population; Diagnosed with substance dependence; or diagnosed with substance use disorder; or no diagnosis with recurrent use of psychoactive substances	Animal models excluding human population; Neurocomputational models excluding human population; Other addictions (gambling, internet, gaming, etc.)
<b>Intervention</b>	Neuropsychological assessment measures of (a) executive functioning; or (b) general cognition with executive function as a subcomponent. Or (c) attention; or (d) working memory; or (e) decision making as subcomponents of executive functioning	Neuroimaging, biochemical or genetic methods excluding neurocognitive assessment measures.
<b>Comparator</b>	All	None
<b>Outcomes</b>	All	None
<b>Study design</b>	Randomised control trials Non-randomised control trials Cohort studies Case control studies Case series studies Cross-sectional studies Non-comparative studies Other (e.g. multi-method)	Qualitative exclusively
<b>Setting</b>	All	None
<b>Language</b>	All	None
<b>Period</b>	All	None
<b>Ethics</b>	Ethical conduct	Ethical violations*

\* Harm, coercion, deception, breach of privacy and confidentiality, fabrications, omissions and contrivances.

Except for purely qualitative studies, all other types of study designs will be included in the proposed systematic review. However, qualitative studies may provide valuable insights and will be consulted after the narrative synthesis to possibly further contextualise the findings.

Studies that were conducted in any setting will be included. These may be rehabilitation facilities, rural clinics, outpatient clinics, private practices and hospitals.

Ethical violation will be considered an exclusion criterion. This includes any form of harm, coercion, deception, breach of privacy and confidentiality, fabrications, omissions and contrivances (Wagner, Kawulich, & Garner, 2012).

Studies with null or negative findings are more likely to be published in non-English language journals (Boland et al., 2017). Therefore, studies in all languages will be included to account for language bias. The English versions of these studies will be requested from the authors. If this is not available, the studies will be submitted to Cochrane Task Exchange for translation. All efforts will be made to include these studies. However, it is important that this process does not significantly delay the timeframes of the overall project.

Studies with null or negative findings are less likely to be submitted or selected for publication in peer-reviewed journals (Boland et al., 2017). To account for publication bias, studies from both peer-reviewed and non-peer-reviewed journals will be included.



The screening and selection strategy is as follows:

1. **Screening and selection will be piloted** on several titles and abstracts by two reviewers independently using the inclusion and exclusion criteria (Table 3).
2. The two reviewers will discuss the results and **identify any differences and reasons for these differences**. Where differences indicate problems with the predefined criteria, the necessary corrections will be made. All efforts will be made to find common ground where subjectivity is the reason for differences. Differences and consensus will be reported to the supervisor of the study to ensure the risk of bias is monitored.
3. When consensus is reached **the inclusion and exclusion criteria will be loaded onto Covidence**. This enables quick reference to the criteria while screening.  
**Specific keywords will be programmed on Covidence**. During the screening, keywords related to inclusion criteria will be highlighted in green and keywords related to the exclusion criteria will be highlighted in red.
4. **All titles and abstracts will be screened on Covidence by the two reviewers**. All voting is blinded on Covidence to ensure voting is not biased. The possible options to choose from are: *Yes* for include, *No* for exclude and *Maybe* for uncertain. A reason for the selected option must be provided in the customised dropdown list or *Notes* field. All studies need a vote from both reviewers before final categorisation.
5. When screening is completed, **studies will be categorised in Covidence** as *Included* (Yes and Yes/Yes and Maybe), *Excluded* (No and No) and *Resolve Conflict* (Yes and No/No and Maybe).
6. **Conflict will be resolved** by discussing the reasons for differences and reaching consensus. Differences and consensus will be reported to the supervisor of the study to monitor bias.
7. From the included studies, **full-text papers will be obtained** from the Unisa Library. Where full-text papers are not located through the Unisa Library, an information scientist will be consulted to assist with obtaining these papers through the interlibrary loan system or the papers will be requested from the authors directly. All efforts will be made to obtain full-text papers. However, it is important that the overall project is not significantly delayed.
8. The **full-text papers of each included study will be uploaded to Covidence**
9. The **full-text papers will be screened by the two reviewers** on Covidence.
10. Any **differences will be resolved**. Differences and consensus will be reported to the supervisor of the study to monitor bias.
11. **Included studies are transferred to the Extraction module** in Covidence.

The entire screening and selection process will be illustrated using the PRISMA flow diagram (Moher, Liberati, Tetzlaff, & Altman, 2009)

### **Data extraction**

Data related to the study characteristics and the participants are required to answer the review questions. More specifically, it will be necessary to extract the following information from each included study:

- The substance(s) used by participants.
- The demographic details of the participants.
- The specific neuropsychological measures that were used to assess executive functions.
- The results of the neuropsychological assessment. This will include the general results of the groups within each study (if applicable) and the results of the respective measures used in each study (if applicable).
- The comparators within the studies (if applicable). For example, the results of assessment may be compared between two or more groups.
- The settings where assessments were conducted. For example, rehabilitation hospital or out-patient clinic.
- The study design used.

The preliminary list of data types that will be extracted is tabulated in a data extraction form (Table 4). However, the data extraction table may be modified based on the available data in the included studies. This will ensure the most appropriate data is extracted to answer the review questions.

**Table 4:** Data extraction form

<b>Paper ID</b>	
<b>Author(s)</b>	
<b>Title</b>	
<b>Journal</b>	
<b>Year</b>	
<b>Reviewer</b>	
<b>Date</b>	
<b>Linked publications</b>	
<b>Study characteristics</b>	<b>Participants/Groups</b>
Study design	Age
Country	Age initial use
Study period	Substance(s)
Number of participants (including dropouts)	Years of use
Intervention(s) (assessment measures)	Treatment attempts
Comparator(s) (e.g. control versus experimental)	Gender
Baseline	Ethnicity
Outcomes (assessment results for each group)	Language
Outcomes (assessment results for each measure)	Income status
Sponsorships	Work experience/Employment status
	Criminal history
	Educational level/Years of education
	Mental and health status
	Notes:

The data extraction strategy will be as follows:

1. The **data extraction form will be piloted by two independent reviewers**. This is to ensure the data fields and formats are accurate in terms of the available and required data.
2. A **second pilot will be conducted** to ensure the same data is extracted by the two reviewers.
3. Any **inconsistencies will be resolved before conducting the full data extraction** by discussing the differences and reaching a mutual understanding. The review questions and protocol will serve as the primary guideline to resolve differences. Differences and consensus will be reported to the supervisor to ensure the risk of bias is monitored.
4. The **extraction module on Covidence will be customised** with the appropriate data fields and formats.
5. The **two reviewers will independently conduct data extraction** on Covidence. A data extraction form will be completed with the relevant data from each study. All extracted data will be highlighted and saved in the PDF document of the study paper.

### ***Quality assessment***

The important elements that will be considered in the quality assessment of studies include selection bias, allocation bias, performance bias, detection bias, attrition bias, reporting bias, confounders, concurrent/subsequent interventions, analysis and funding bias (Boland et al., 2017)

Quality assessment (QA) is carried out after data extraction to ensure the reviewers are familiar with the specific data and thereby better able to identify quality aspects of the studies.

The designs of the included studies will be considered to determine the specific QA tool(s) that will be used. There are various types of quality assessment tools available. Common types of designs that may be present and included in the systematic review are randomised controlled treatments, non-randomised controlled treatments, cohort of which both prospective and retrospective (with or without a control group), case control, case series and cross-sectional.

The chosen QA tools have been listed for the various designs in Table 5. All design types can be assessed using checklists by the Critical Appraisal Skills Programme (2018) or the Study Quality Assessment by Zaza et al. (2000). Notably, the Health Technology Assessment report (Deeks et al., 2003) considers the Study Quality Assessment a suitable measure in systematic reviews. The results from the quality assessment will be tabulated and summarised and the implications of these results will be discussed in the final presentation.

**Table 5:** Study designs with allocated quality assessment tools

Study design	Quality Assessment Tool
<b>Randomised control trial</b>	CASP Randomised Controlled Trial Checklist or Study Quality Assessment
<b>Non-randomized control trial</b>	Study Quality Assessment
<b>Cohort study</b>	CASP Cohort Study Checklist or Study Quality Assessment
<b>Case control study</b>	CASP Case Control Study Checklist or Study Quality Assessment
<b>Case series study</b>	Study Quality Assessment
<b>Cross-sectional study</b>	Study Quality Assessment
<b>Other</b>	Study Quality Assessment

The quality assessment strategy will be as follows:

1. The **Quality Assessment module in Covidence will be customised** according to the fields and option formats of the quality assessment tools (Table 5)
2. **Each study will be quality assessed by two reviewers.** Close-ended questions will be presented in the assessment with judgement options of either *Yes*, *No* or *Unclear*. Justification of the selected option will be highlighted in the PDF and the text will be copied to the *Judgement Notes*.
3. **Quality assessment results are summarised** and the risk of bias for each study is graded as either Low, High or Unclear.

### ***Analysis and synthesis***

The extracted data of the proposed systematic review is expected to be highly heterogenous in terms of populations, interventions, settings, study designs and outcomes. A meta-analysis is only performed where the data is sufficiently similar and it is sensible to combine the data (Boland et al., 2017). Therefore, the primary aim is to provide a narrative synthesis of the available data which is also appropriate to answer the review questions.

The data from the data extraction forms of individual studies will be combined in data extraction tables using Microsoft Excel. Subsequently, the data will be analysed using descriptive statistics to describe and summarise the gathered information. By this means, adequate comparisons can be made to identify possible consensus or near-consensus findings and inconsistencies. Subsequently, it may be likely to uncover exhaustive evidence and gaps in the available research.

### ***Presentation***

The full systematic review will be presented in the form of a full dissertation as required for the intended degree. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses



(PRISMA) will be used as the primary guideline for the presentation of this systematic review (Moher et al., 2009).

### **Ethics**

The proposed research study is a systematic review and therefore no participants will be sampled. The ethical considerations of each included study of the proposed review will be assessed during the quality assessment. Only research studies conducted ethically will be included in this review.

The ethical guidelines and procedures set out by the University of South Africa (2016) and the Department of Health (2015) will be adhered to at all times.

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## Appendix B: Ethics Approval



### COLLEGE OF HUMAN SCIENCES RESEARCH ETHICS REVIEW COMMITTEE

30 April 2019

Dear Jacques Jansen van Vuuren

NHREC Registration # :

Rec-240816-052

CREC Reference # : 2019-

CHS-Depart-4387-622-6

**Decision:**

**Ethics Approval from 30 April  
2019 to 01 May 2023**

**Researcher(s): Jacques Jansen van Vuuren**

**Supervisor(s): Prof Martin Terre Blanche**

**terremj@unisa.ac.za**

**Neuropsychological assessment of executive functions in substance  
dependence populations: a systematic review**

**Qualification Applied: Research Masters in Psychology**

Thank you for the application for research ethics clearance by the Unisa Department of Psychology College of Human Science Ethics Committee. Ethics approval is granted for three years.

The **low risk application** was **reviewed and expedited** by Department of Psychology College of Human Sciences Research Ethics Committee, on the **(30 April 2019)** in compliance with the Unisa Policy on Research Ethics and the Standard Operating Procedure on Research Ethics Risk Assessment.

The proposed research may now commence with the provisions that:

1. The researcher(s) will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.



University of South Africa  
Preller Street, Muckleneuk Ridge, City of Tshwane  
PO Box 392 UNISA 0003 South Africa  
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150  
[www.unisa.ac.za](http://www.unisa.ac.za)

2. Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study should be communicated in writing to the Department of Psychology Ethics Review Committee.
3. The researcher(s) will conduct the study according to the methods and procedures set out in the approved application.
4. Any changes that can affect the study-related risks for the research participants, particularly in terms of assurances made with regards to the protection of participants' privacy and the confidentiality of the data, should be reported to the Committee in writing, accompanied by a progress report.
5. The researcher will ensure that the research project adheres to any applicable national legislation, professional codes of conduct, institutional guidelines and scientific standards relevant to the specific field of study. Adherence to the following South African legislation is important, if applicable: Protection of Personal Information Act, no 4 of 2013; Children's act no 38 of 2005 and the National Health Act, no 61 of 2003.
6. Only de-identified research data may be used for secondary research purposes in future on condition that the research objectives are similar to those of the original research. Secondary use of identifiable human research data require additional ethics clearance.
7. No fieldwork activities may continue after the expiry date **(01 May 2023)**. Submission of a completed research ethics progress report will constitute an application for renewal of Ethics Research Committee approval.

*Note:*

*The reference number **2019-CHS--Depart-4387-622-6** should be clearly indicated on all forms of communication with the intended research participants, as well as with the Committee.*

Yours sincerely,

Signature :



Prof I. Ferns  
Ethics Chair: Psychology  
Email: [fernsi@unisa.ac.za](mailto:fernsi@unisa.ac.za)  
Tel: (012) 429 8210

Signature :



Dr Suryakanthie Chetty  
Ethics Chair : CREC  
E-mail: [chetts@unisa.ac.za](mailto:chetts@unisa.ac.za)  
Tel: (012) 429 6267



University of South Africa  
Preller Street, Muckleneuk Ridge, City of Tshwane  
PO Box 392 UNISA 0003 South Africa  
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150  
[www.unisa.ac.za](http://www.unisa.ac.za)